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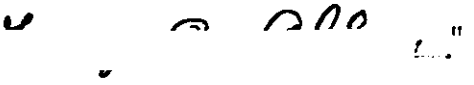

SPIROPIPERIDINE THIOBARBITURIC ACIDS

A THESIS

Presented to

the Faculty of the Graduate Division

by

George Cyrus Allen

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

January, 1961

SPIROPIPERIDINE THIOBARBITURIC

ACIDS

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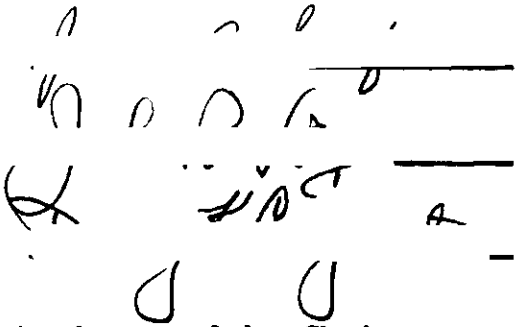

Date Approved by Chairman:

February 8, 1961

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ABSTRACT

The purpose of this research was to prepare spiropiperidine-4',5-(2-thiobarbituric) acids. Although three approaches to the syntheses of these compounds were investigated, only two were successful. A number of the desired thiobarbituric acids were prepared and characterized (Table 2).

One of the methods of synthesis investigated started with 4,4-dicarbethoxytetrahydropyran. This diester was condensed with thiourea to yield spirotetrahydropyran-4',5-(2--thiobarbituric) acid. It was hoped that the ether linkage of the tetrahydropyran ring could be cleaved with hydrogen iodide to yield 5,5-bis(2-iodoethyl)-2-thiobarbituric acid. If such could be achieved, then condensation of this compound with various primary amines would form the piperidine ring thus giving the desired compound. The cleavage of the tetrahydropyran ether linkage was unsuccessful.

The other methods investigated were concerned largely with the synthesis of 1-substituted-4,4-dicarbethoxypiperidines (see Table 1) and their condensation with thiourea. In the first method of synthesis, bis(2-hydroxyethyl)amines were reacted with thionyl chloride or p-toluenesulfonyl chloride to form the bis(2-chloroethyl)amines. These sub-

stances when condensed with diethyl malonate would yield the desired diesters. This method was successful for the synthesis of 1-phenyl- and 1-m-tolyl-4,4-dicarbethoxypiperidines but was unsuccessful in the synthesis of 4,4-dicarbethoxypiperidine itself.

A second method of synthesis of 1-alkyl-4,4-dicarbethoxypiperidines was also successfully investigated. This route started with isonicotinic acid. The acid was first converted to the ethyl ester which was then reacted with alkyl halides to give 1-alkyl-4-carbethoxypyridinium halides. Catalytic hydrogenation of these salts yielded 1-alkyl-4-carbethoxypiperidines. The reaction of these esters with ethyl chloroformate in the presence of triphenylmethylsodium afforded 1-alkyl-4,4-dicarbethoxypiperidines in good yields. 1-Methyl-, 1-ethyl-, 1-iso-propyl-, 1-n-butyl-, and 1-benzyl-4,4-dicarbethoxypiperidines were prepared by this method.

Condensation of the diesters with thiourea in the presence of sodium ethoxide to obtain the disodium salt of the spiropiperidine thiobarbituric acids was accomplished in good yields. Neutralization with an ion exchange resin afforded the 1'-aryl acids in good yields but gave poor yields for the 1'-alkyl acids.

Ultraviolet spectra of the spiropiperidine-4',5-(2-thiobarbituric) acids in 1 N sodium hydroxide showed an absorption maximum at about 274 millimicrons which decreased rapidly. This band is due to the dianion. Spiro-1'-alkyl-

piperidine-4',5-(2-thiobarbituric) acids show an absorption maximum at about 288 millimicrons in distilled water; this is probably due to the zwitterionic form of these compounds. The 1'-aryl acids showed no absorption in this area when saturated aqueous solutions were used.

Infrared spectra of intermediates and the spiropiperidine thiobarbituric acids were recorded. These spectra also indicate a zwitterionic structure for the 1'-alkyl spiropiperidine thiobarbituric acids but not for the 1'-aryl acids.

Recommendations for the synthesis of spiropiperidine thiobarbituric acids with substituents on both rings and the spiro atom at a different position of the piperidine ring were made.

CHAPTER I

INTRODUCTION

The purpose of this research was to investigate methods of preparation of thiobarbituric acids containing a spiropiperidine ring. Since other thiobarbituric acids are useful hypnotics, it was believed that these compounds might possess desirable physiological properties.

In 1905 Merck (1) obtained a patent for the preparation of 5,5-dialkyl-2-thiobarbituric acids (Figure 1, a and b) from dialkyl malonyl chlorides and thiourea. A few years later, in 1908, Einhorn and von Diesbach (2) prepared a number of 5,5-dialkyl-2-thiobarbituric acids (Figure 1, a-e), by the condensation of diethyl 5,5-dialkylmalonates with thiourea in the presence of sodium ethoxide.

While neither Merck (1) nor Einhorn (2) reported having studied the pharmacological properties of these materials, Tabern and Volwiler (3), in repeating and extending the work of Einhorn and von Diesbach, prepared

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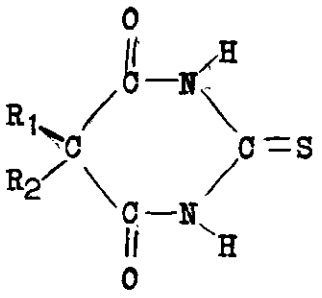
(1) E. Merck, German Patent 182,764,(April 5, 1905), Chem. Zentr., 78, 1648 (1907).

(2) A. Einhorn and H. von Diesbach, Ann., 359, 145 (1908).

(3) D. L. Tabern and E. H. Volwiler, J. Am. Chem. Soc., 57, 1961 (1935).



	R_1	R_2
a.	C_2H_5-	C_2H_5-
b.	$(CH_3)_2CH$-	$(CH_3)_2CH$-
c.	CH_3-	CH_3-
d.	CH_3-	C_2H_5-
e.	C_2H_5-	C_2H_5-
f.	C_2H_5-	$CH_3CH_2(CH_3)CH$-
g.	$CH_2=CHCH_2$-	$CH_2=CHCH_2$-
h.	C_2H_5-	$CH_2=CHCH_2$-

Figure 1. 5,5-Disubstituted-2-thiobarbituric Acids

other 5,5-disubstituted-2-thiobarbituric acids (Figure 1, a-f). The pharmacological action of these compounds was studied; thus, it was found that the thio compounds were more active as hypnotics than the corresponding oxygen analogs, but were also more toxic. Nevertheless, favorable effective-to-toxic dose ratios were found. It was also noted that the duration of hypnosis was shorter with the sulfur compounds than with the oxygen analogs (3).

This work stimulated much research which resulted in the synthesis and physiological investigation of many hitherto unknown thiobarbituric acids. Doran has tabulated the properties of more than five-hundred thiobarbituric acids (4). Dundee has written a comprehensive treatise

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(4) W. J. Doran, Medicinal Chemistry, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1959, pp. 204-237.

on thiopentone[1] and similar compounds (5).

A number of spirocarbocylic thiobarbituric acids have also been prepared. Spirocyclobutane-1',5-(2-thiobarbituric) acid (Figure 2) was prepared from 1,1-dicarbethoxycyclobutane and thiourea by Dox and Yoder (6); however, no mention of the pharmacology of this material was made.

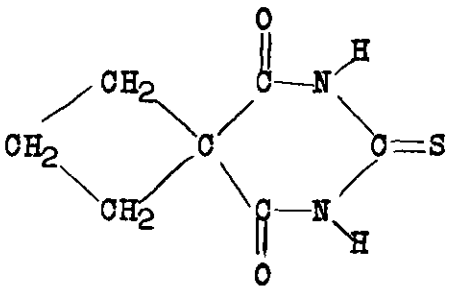

Figure 2. Spirocyclobutane-1',5-(2-thiobarbituric) Acid

Later, Doran and van Heyningen (7) obtained a patent for the synthesis of 1,1-dicarbethoxycyclopentanes from 1,4-dibromo butanes and diethyl malonate using sodium ethoxide. They also obtained a patent (8) for the alkoxide

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[1]Refers to sodium 5-ethyl-5(1-methylbutyl)-2-thiobarbiturate.

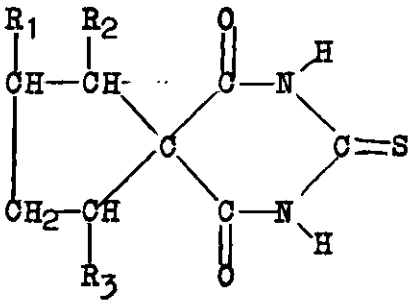
(5) J. W. Dundee, Thiopentone and Other Thiobarbiturates, E. and S. Livingstone Ltd., London, 1956.

(6) A. W. Dox and L. Yoder, J. Am. Chem. Soc., 43, 677 (1921).

(7) W. J. Doran and E. van Heyningen, U. S. Patent 2,561,688, (March 23, 1948).

(8) Ibid., U. S. Patent 2,561,689, (March 24, 1948).

catalyzed condensation of these diesters with thiourea to yield spirocyclopentane-1',5-(2-thiobarbituric) acids (Figure 3). These materials apparently were not tested for physiological activity.



	R_1	R_2	R_3
a.	H	C_2H_5	C_2H_5
b.	CH_3	C_2H_5	C_2H_5

Figure 3. Spirocyclopentane-1',5-(2-thiobarbituric) Acids

Cope et al. (9) obtained various alkylated 1,1-dicarbethoxycyclohex-3-enes from the reaction of alkylidene malonic esters with 1,3-dienes. These diesters could be hydrogenated to the corresponding 1,1-dicarbethoxycyclohexanes. Both the saturated and unsaturated diesters were allowed to react with thiourea to give spirocyclohexane-1',-5-(2-thiobarbituric) acids (Figure 4) and spirocyclohex-3'-ene-1',5-(2-thiobarbituric) acids (Figure 5), respectively. E. van Heyningen (10) also reported the synthesis of some spirocyclohexane-1',5-(2-thiobarbituric)

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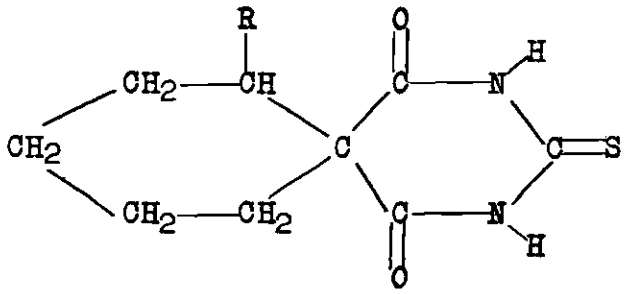
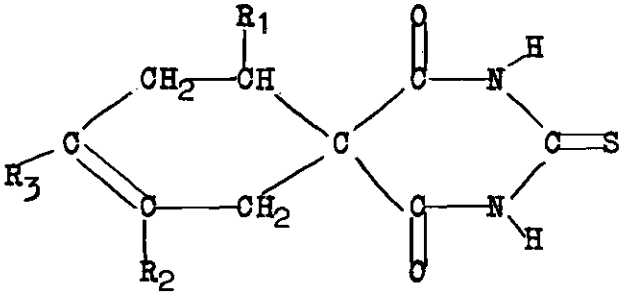
(9) A. C. Cope, P. Kovacic, and M. Burg, J. Am. Chem. Soc., 71, 3658 (1949).

(10) E. van Heyningen, J. Am. Chem. Soc., 76, 2241 (1954).



R = H, CH_3, C_2H_5, n-C_3H_7

Figure 4. Spirocyclohexane-1',5-(2-thiobarbituric) Acids



	R_1	R_2	R_3
a.	H	H	H
b.	CH_3	H	H
c.	C_2H_5	H	H
d.	n-C_3H_7	H	H
e.	CH_3	CH_3	CH_3

Figure 5. Spirocyclohex-3'-ene-1',5-(2-thiobarbituric) Acids

acids but made no report of having studied the pharmacology of the compounds. On the other hand, Cope (9) reported that both spirocyclohex-3'-ene-1',5-(2-thiobarbituric) acids and spirocyclohexane-1',5-(2-thiobarbituric) acids were less active and had poorer therapeutic ratios than the corresponding oxygen analogs.

At the beginning of this research, the only thiobarbituric acid containing a hetero atom in a spiro ring was spirotetrohydropyran-4',5-(2-thiobarbituric) acid

(Figure 6.) which was reported by Daugherty (11). This compound was not tested for physiological activity.

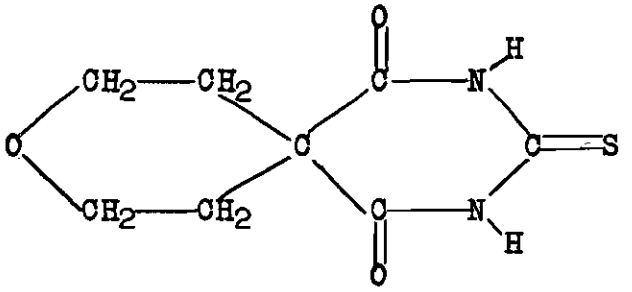


Figure 6. Spirotetrahydropyran-1',5-(2-thiobarbituric) Acid

The presence of a cyclic nitrogen atom in alkaloids is a distinct feature of these physiologically active compounds. A number of alkaloids, for example, morphine, codiene, and thebaine contain a piperidine ring. Furthermore, the piperidine ring in these substances is not in the same plane as the rings to which it is attached. A similiar situation exists with the spiropiperidine-4',5-barbituric acids (Figure 7.). The piperidine ring is a spiro ring and is non-planar with the barbiturate ring. Such features could have significant effect upon the physiological activity of the molecule and could convey to it unusual characteristics.

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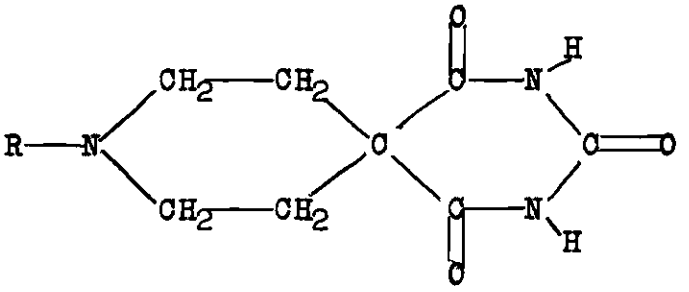
(11) P. M. Daugherty, Unpublished Ph.D. Thesis, Georgia Institute of Technology, 1957, p. 83.



R		R	
a.	Methyl	g.	Cyclohexyl
b.	Ethyl	h.	Benzyl
c.	2-Hydroxyethyl	i.	o-Tolyl
d.	iso-Propyl	j.	p-Tolyl
e.	n-Butyl	k.	2-Phenylethyl
f.	Phenyl	l.	n-Propyl

m. Benzenesulfonyl

Figure 7. Spiropiperidine-4',5-barbituric Acids

Spiropiperidine-4',5-barbituric acids (Figure 7, a-k) have been synthesized by Stanfield and Daugherty (12). These were not prepared from 4,4-dicarbethoxypiperidines but from 5,5-bis(2-iodoethyl)-barbituric acid and primary amines. Büchi and co-workers (13) used a similiar technique to prepare three spiropiperidine-4',5-barbituric acids (Figure 7,

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(12) J. A. Stanfield and P. M. Daugherty, J. Am. Chem. Soc., 81, 5167 (1959).

(13) J. Büchi, K. Levenburger, and R. Lieberherr, Farm. Sci. e tec., (Pavia) 6, 429 (1951). C. A., 46, 8015 (1952).

a, e and 1). Both workers (12, 13) reported that the compounds were not hypnotic when administered to white rats.

While no hypnotic action was observed with these compounds, this does not preclude that the sulfur analogs could not be active. It has been shown that the replacement of an oxygen atom by a sulfur atom in the 2-position of a barbituric acid can enhance[1] or decrease[2] the physiological activity of the substance depending on the rest of the molecule. In addition it should be mentioned that Skinner et al. (14) synthesized spiro-1'-benzenesulfonylpiperidine-4',5-barbituric acid (Figure 7, m) and found that it was not hypnotic to test animals but induced convulsions.

Thus, it appeared to be of interest to synthesize spiropiperidine-4',5-(2-thiobarbituric) acids (Figure 8).

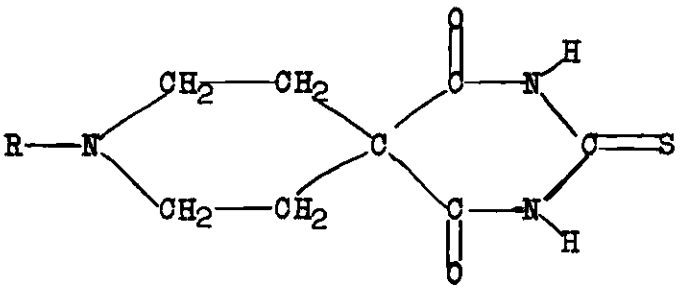

Figure 8. Spiropiperidine-4',5-(2-thiobarbituric) Acid

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[1]See page 2 above and reference (3).

[2]See page 5 above and reference (9).

(14) G. Skinner, H. Krysiak, and J. Perregrino, J. Am. Chem. Soc., 77, 2248 (1955).

CHAPTER II

DISCUSSION OF EXPERIMENTAL INVESTIGATIONS

Three routes leading to spiropiperidine-4',5-(2-thiobarbituric) acids were investigated. One, which was not successful, was essentially that used by Daugherty (11) for the preparation of spiropiperidine-4',5-barbituric acids. An outline of this route is diagrammed in Figure 9. This sequence of reactions starts with bis(2-chloroethyl) ether which was condensed with diethyl malonate to yield 4,4-dicarbethoxytetrahydropyran (Figure 9, I) (15). Condensation of 4,4-dicarbethoxytetrahydropyran with thiourea in tert-butyl alcohol using tert-butoxide ion as a base afforded spirotetrahydropyran-4',5-(2-thiobarbituric) acid in good yield. All attempts to cleave the ether linkage of II with phosphoric acid and potassium iodide failed (Figure 9, (c)). Only black tar resulted from the reaction and large quantities of hydrogen sulfide were evolved as the reaction proceeded. Investigation via procedure I was discontinued in favor of pursuing more promising routes to the desired thiobarbituric acids.

The investigation at this point was concentrated on a method of synthesis of 1-substituted-4,4-dicarbethoxy-

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(15) G. H. Harnest and A. Burger, J. Am. Chem. Soc., 65, 370 (1943).

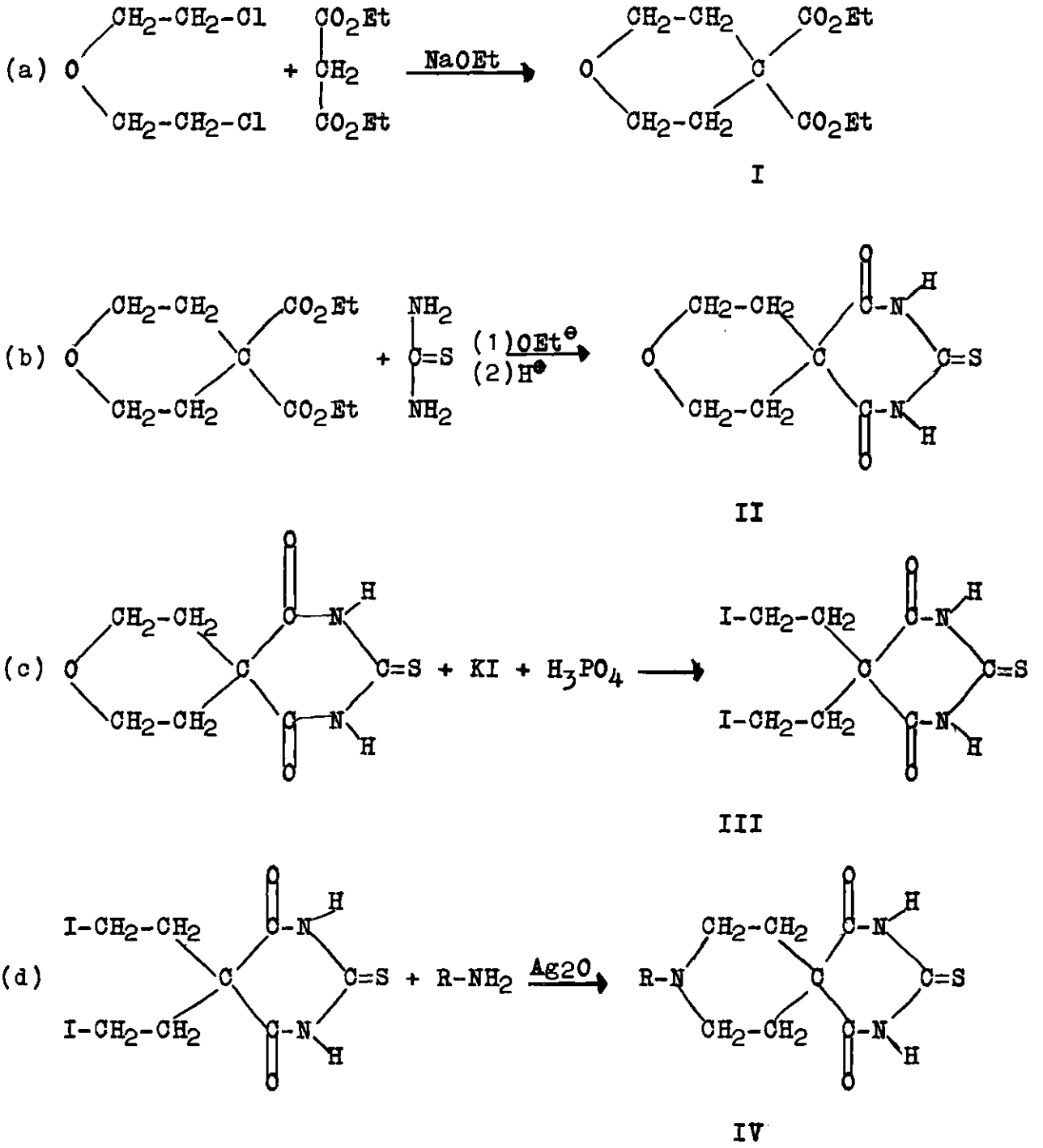

Figure 9. Proposed Synthesis of Spiropiperidine-4',5-(2-thiobarbituric) Acids (Procedure I)

piperidines (Table 1). It was concluded that if these could be prepared then little difficulty should be encountered in condensing them with thiourea to give spiropiperidine-4',5--(2-thiobarbituric) acids. One general route to the piperidine derivatives, outlined in Figure 10, involved the preparation of nitrogen mustards or ditosylates[1] of diethanolamines, and the subsequent condensation of these with diethyl malonate. Similiar reactions are not without precedent, the preparation of 4,4-dicarbethoxytetrahydropyran from bis(2-chloroethyl) ether and diethyl malonate being one[2]. In a like manner, thiophene acetonitriles have been condensed with nitrogen mustards to produce compounds containing a piperidine ring. For example, 2-[4'-(1'-methyl-4'cyanopiperidyl)] thiophene was prepared by the condensation of bis-(2-chloroethyl)methylamine and 2-cyanomethylthiophene (16). Sodium ethoxide and sodium amide were the bases used in these respective examples.

The simplest case tried in the present work, bis(2-chloroethyl)amine, was prepared by the action of thionyl chloride on diethanolamine followed by treatment with sodium hydroxide to yield the free base. Attempts to condense this material with diethyl malonate in ethanol with ethoxide and in toluene

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[1]Refers to the di-p-toluenesulfonic esters.

[2]See above, page 9 and reference (15).

(16) F. F. Blicke, U. S. Patent 2,425,721 (August 19, 1947).

Table 1. 4,4-Dicarbethoxypiperidines

4,4-Dicarbethoxypiperidine	B.P. °C	Mm
1-Methyl-	86-89	2[1]
1-Ethyl-	91-92	0.4
1-iso-Propyl-	103-105	0.1
1-n-Butyl-	113-114	0.1
1-Benzyl-	165-167	0.2
1-(2-phenylethyl)-	162-163	0.1
1-Phenyl	158-160	3[2]
1-m-Tolyl	187-188	3[3]

[1] J. Schmutz, F. Kunzle, and R. Hirt, Helv. Chim. Acta 37, 1772 (1954) report b.p. 134-137°/12 mm.

[2] R. Anker, A. H. Cook, and I. M. Hielbron, J. Chem. Soc., 1917 (1945) report 140°/4 mm.

[3] W. H. Starnes, Unpublished Ph.D. Thesis, Georgia Institute of Technology, 1960, p. 73.

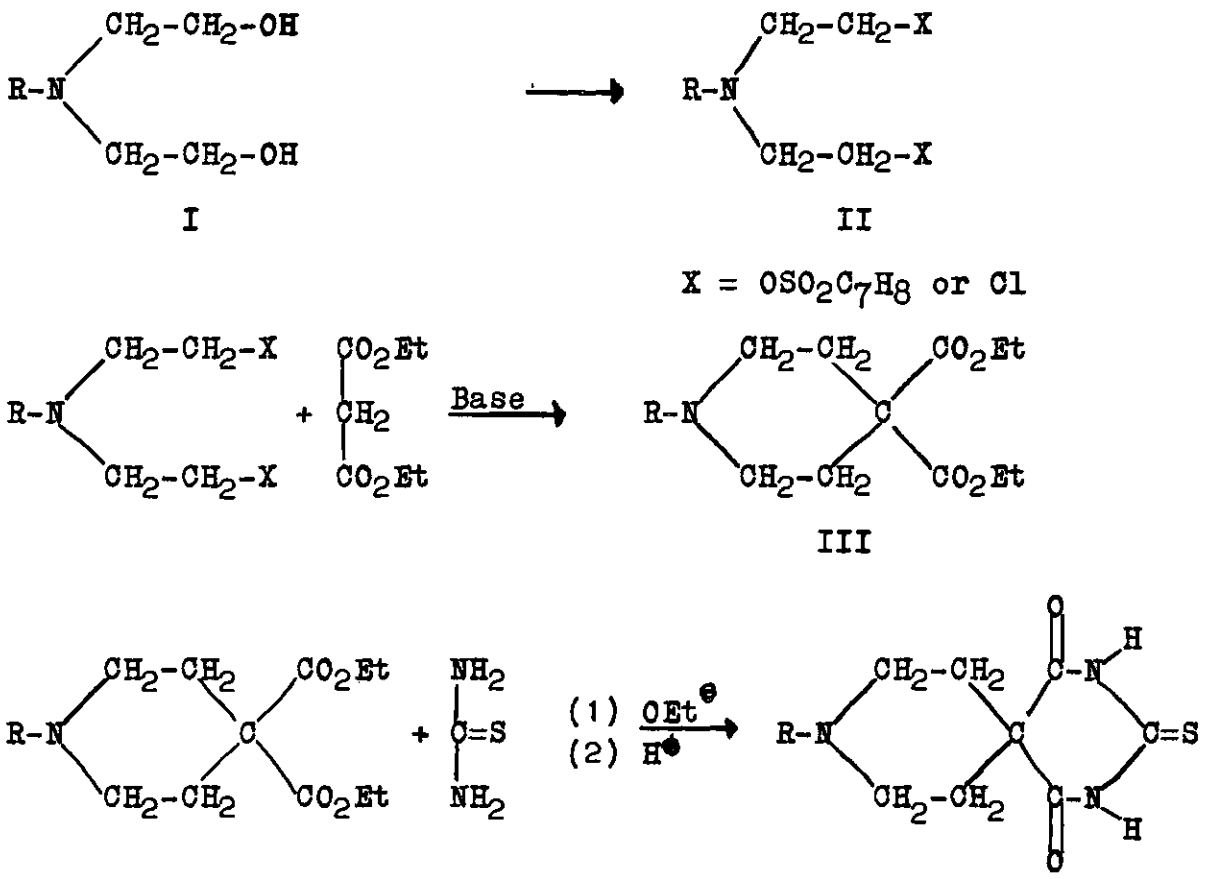

Figure 10. Proposed Synthesis of Spiropiperidine-4',5-(2-thiobarbituric) Acid (Procedure II)

with sodium both failed. Although tars were obtained in both cases good recovery of diethyl malonate was possible.

Starnes (17) attempted a similiar sequence of reaction with methyl diethanolamines. These did not meet with success. The failure of this sequence was in reaction (b) (Figure 10.) i.e. the nitrogen mustards failed to condense with diethyl

(17) W. H. Starnes, Unpublished Ph.D. Thesis, Georgia Institute of Technology, 1960, p. 110.

malonate. This failure is probably due to the nucleophilicity of the nitrogen atom which could give rise to intra- or intermolecular reactions leading to polymers, piperazinium dimers or imine salts (18).

Bartlett et al. (19) found that bis(2-chloroethyl)methylamine was transformed (85 per cent) into 1,4-dimethyl-1,4--bis(2-chloroethyl)piperazinium dichloride by letting the amine stand in absolute ethanol. Sprague et al. (20) reported that bis(2-p-toluenesulfonyloxyethyl)alkylamines could not be isolated.

Anker et al. (21) prepared 1-phenyl-4,4-dicarbethoxypiperidine from bis(2-chloroethyl)phenylamine and diethyl malonate using sodium in toluene as the condensing medium. When this was repeated, difficulty in separation of the product from unreacted starting material was encounted. Investigation showed that the use of the ditosylate of phenyldiethanolamine in place of bis(2-chloroethyl)phenylamine gave good yields of 1-phenyl-4,4-dicarbethoxypiperidine (Figure 10, III,

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(18) For a discussion of this type of reaction see J. Hine, Physical Organic Chemistry, McGraw-Hill Book Co., Inc., New York, N. Y., Chapter 5, Section 4 also Chapter 6, Section 3 and references cited therein.

(19) P. D. Bartlett, S. D. Ross, and C. Swain, J. Am. Chem. Soc., 69, 2971 (1947).

(20) J. M. Sprague, D. Hill, and E. Engelhardt, U. S. Patent 2,671,105 (May 1, 1954).

(21) R. M. Anker, A. H. Cook, and I. M. Heilbron, J. Chem. Soc., 1917 (1945).

R = C_6H_5). The 1-m-tolyl-4,4-dicarbethoxypiperidine was also prepared. The success of this reaction can be attributed to the decreased nucleophilicity of aryl amines compared to alkyl amines.

Spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid was prepared by the condensation of thiourea with 1-phenyl-4,-4-dicarbethoxypiperidine in the presence of sodium ethoxide. The disodium salt was acidified by passing dry hydrogen chloride into a suspension of the salt in absolute ethanol. The yield was improved somewhat when an ion exchange resin, Amberlite IRC-50, a carboxylic acid resin, was used in absolute ethanol. Spiro-1'-m-tolylpiperidine-4',5-(2-thiobarbituric) acid was likewise prepared.

Another approach to 1-alkyl-4,4-dicarbethoxypiperidines, Procedure III, is outlined in Figure 12. This procedure starts with pyridine-4-carboxylic acid, commonly known as isonicotinic acid. The acid was first esterified with ethanol using sulfuric acid as a catalyst. The water formed was removed with anhydrous magnesium sulfate in the thimble of a Soxhlet extractor (22). N-Alkyl-4-carbethoxypyridinium halides (Figure 12, III) were then prepared by refluxing ethyl isonicotinate with various alkyl halides in absolute ethanol. In this manner methyl iodide was successfully used. While the ethyl iodide salt could not be purified so that it

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(22) M. Pailer, K. Schneylberger, and W. Reifschneider, Monatsh. Chem., 83, 513 (1952).

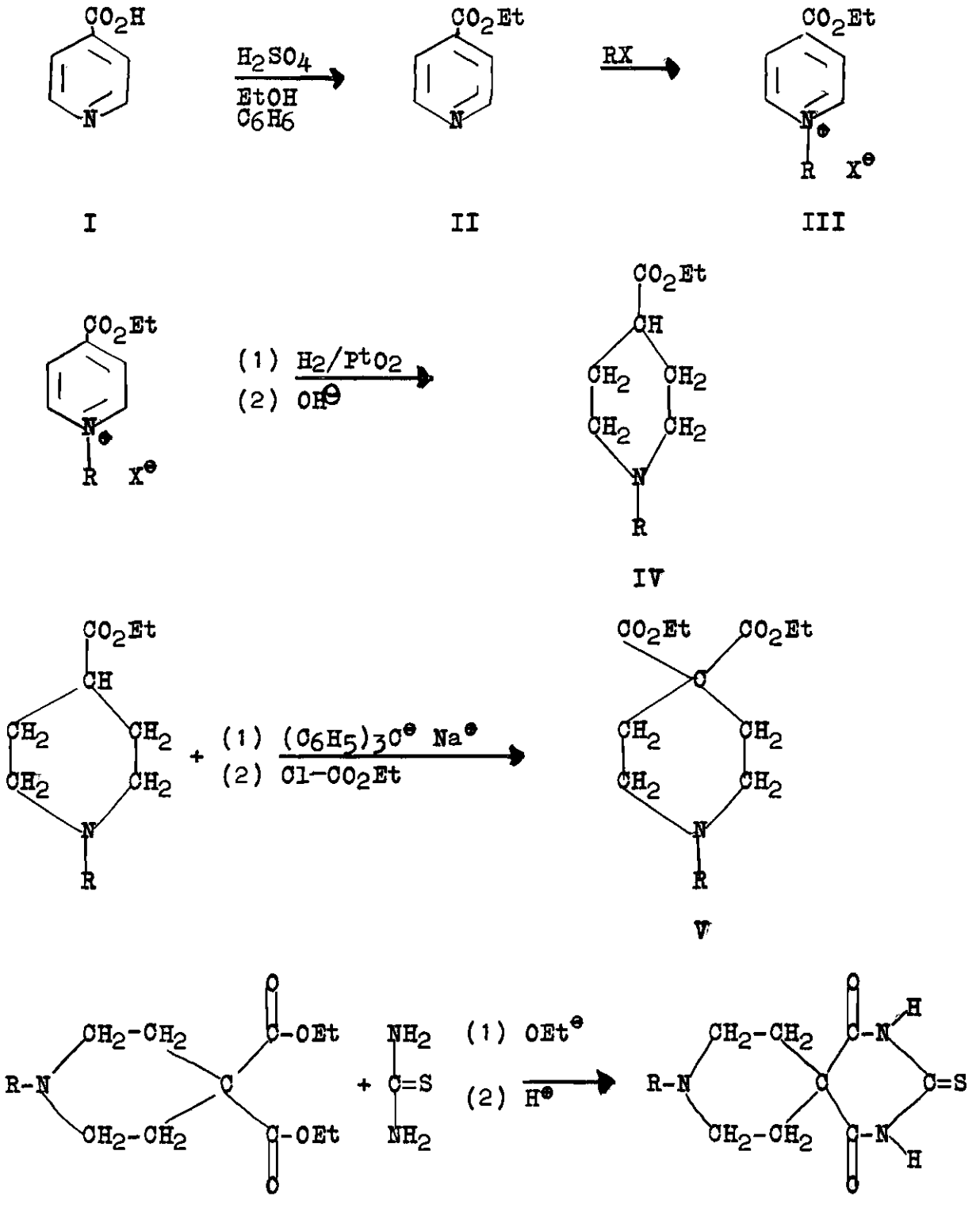

Figure 11. Proposed Synthesis of Spiropiperidine-4',5-(2-thiobarbituric) Acid (Procedure III)

could be hydrogenated, 1-ethyl-4-carbethoxypyridinium bromide, iso-propyl bromide, and benzyl chloride were also reacted with ethyl isonicotinate to give the corresponding salts in excellent yields. β-Phenylethyl chloride failed to react with ethyl isonicotinate but since 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine became available via another route[1] this reaction was not investigated further.

Catalytic hydrogenation of the pyridinium salts, effected in absolute ethanol with platinum dioxide catalyst, yielded the corresponding piperidine salts. These could then be treated with sodium hydroxide to afford the free amine (23). The final step was the carbethoxylation of the isonipocotic esters (Figure 12, IV).

Malonic esters have been prepared from monoesters having two hydrogen atoms on the alpha carbon atom with diethyl carbonate and sodium ethoxide (24). However, this reaction fails when one alpha hydrogen is replaced by an alkyl group. Decreased acidity of the remaining hydrogen is apparently the cause for failure. Consequently, when a stronger base is employed carbethoxylation of esters with a single alpha proton can be made to occur. Accordingly, Hudson and Hauser have carbethoxylated ethyl isobutyrate in

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[1] See below, page 18.

(23) J. Krapcho, U. S. Patent 2,759,942, (August 21, 1956).

(24) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, J. Am. Chem. Soc., 63, 2056 (1941).

yields as high as 75 per cent of theoretical using triphenylmethylsodium as a base and ethyl chloroformate as a source of carbethoxyl groups (25). Triphenylmethylsodium has also been used to remove the 4-proton from 1-methyl-4-carbethoxypiperidine; the resulting carbanion was reacted with benzoyl chloride to give 1-methyl-4-benzoyl-4-carbethoxypiperidine (23).

In view of the preceding facts, carbethoxylation of 1-alkyl-4-carbethoxypiperidine with triphenylmethylsodium and ethyl chloroformate was tried and achieved with good results. Thus, the 1-methyl-, 1-ethyl-, 1-n-butyl-, 1-iso-propyl-, and 1-benzyl-4,4-dicarbethoxypiperidines were prepared in this manner. The 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine was not prepared by this route since β-phenylethyl chloride did not react with ethyl isonicotinate. This does not preclude that the iodide or bromide would not react.

Thweatt (26) prepared 4,4-dicarbethoxypiperidine from 1-benzenesulfonyl-4,4-dicarbethoxypiperidine by reductive cleavage of the sulfur-to-nitrogen bond with hydrogen bromide in glacial acetic acid. Reductive alkylation of 4,4-dicarbethoxypiperidine with phenylacetaldehyde gave 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine in good yield.

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(25) B. E. Hudson and C. R. Hauser, J. Am. Chem. Soc., 63, 3156 (1941).

(26) J. G. Thweatt, private communication.

Spiropiperidine-4',5-(2-thiobarbituric) acids were prepared from the corresponding diesters and thiourea with sodium ethoxide as a catalyst. The sodium salts were isolated but not characterized. They were converted to the acid by stirring with the acid form of a carboxylic acid ion exchange resin in absolute alcohol. The yields of the condensation step were good whereas the yields of the acidification step were dependent on the nature of the spiropiperidine-4',5-(2--thiobarbituric) acid. Thus, the 1'-phenyl- and 1'-m-tolyl-spiropiperidine acids could be acidified in good yields but the 1'-alkyl spiropiperidine acids could be obtained only in low yields. This was perhaps due to salt formation between the resin and the tertiary amine or due to adsorption of the solids on the surface of the resin. The difference in adsorption of the 1'-aryl and 1'-alkyl spiropiperidine acids could be due to a difference in the structure of the two types of compounds. The more polar zwitterionic 1'-alkyl compounds would probably be more strongly adsorbed than the 1'-aryl compounds which do not exist in the zwitterionic structure[1].

The infrared spectra of the thiobarbituric acids and some of the intermediates were recorded using a Perkin-Elmer Infracord Model 137 double beam spectrophotometer. The spectra of the liquids were determined using thin liquid films while those of the solids were made from Mujol mulls. The spectra are reproduced in the appendix.

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[1]See below, page 20.

In the spectra of 1'-phenyl-, 1'-*m*-tolyl-, and 1'-benzyl-spiropiperidine-4',5-(2-thiobarbituric) acids a carbonyl absorption band appeared as a doublet at 5.83±.03 microns and at 5.94±.04 microns. The carbonyl band of the 1'-methyl, 1'-*n*-butyl, 1'-ethyl, and 1'-(2-phenylethyl) compounds appeared in each case as a singlet at 5.90±.01 microns; also, these compounds each had another band at 6.16, 6.25, 6.23, and 6.23 microns, respectively. These latter bands are assigned to >C = N - stretching band and is evidence for a zwitterionic structure (27) (see Figure 13). A band at 6.6±.1 microns which has been assigned to >C = S chromophore in thiobarbituric acids (28) was also observed in these compounds although in some it appeared as a shoulder on the Nujol band at *ca.* 6.9 microns. This salt-like structure is further indicated by the rather high melting points of the spiro-1'-alkylpiperidine-4',5-(2-thiobarbituric) acids.

Since spiropiperidine-4',5-(2-thiobarbituric) acids contain both a basic center and an acidic center it would be expected that they should exist in the zwitterionic form. This is especially true of the 1'-alkyl derivatives since alkyl amines are more basic than aryl amines. The *p*Ka's of 5,5-disubstituted-2-thiobarbituric acids are approximately

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(27) Daugherty, *op. cit.*, p. 17.

(28) L. Levi and C. Hubley, *Perkin-Elmer Instrument News*, *5*, *No. 2*, 6 (1954).

8 (29) while the pKa's of the conjugate acids of 1-alkylpiperidines are 10 (30, 31) and the pKa's of N,N-dialkylanilinium ions are about 5-6[1]. It is apparent, then, that spiro-1'-alkylpiperidine-4',5-(2-thiobarbituric) acids should exist in the inner salt form whereas the spiro-1'-arylpiperidine-4',5-(2-thiobarbituric) acids should not. This difference is basicity of the nitrogen atoms is also reflected in the difference in the methods of synthesis for the two types of spiropiperidine-4',5-(2-thiobarbituric) acids[2].

The ultraviolet spectra of spiropiperidine-4',5-(2-thiobarbituric) acids were recorded in the region from 350-240 millimicrons. In 1 N-sodium hydroxide the compounds exhibited an absorption band at about 274 millimicrons. This band decreased so rapidly that no attempts to calculate an extention coefficient was made. The band is most probably due to the divalent anion of the acids (Figure 13). Daugherty (32) reported a band at 278 millimicrons for spirotetrahydropy-

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[1]While 1-phenylpiperidine would be better for comparison the pKa of this compound was not available. The pKa of 1-phenylpiperidine probably would not differ from the value given above by more than 2 pKa units.

[2]See above, page 13.

(29) H. B. Wood and E. C. Horning, J. Am. Chem. Soc., 75, 5511 (1953).

(30) H. K. Hall, ibid., 79, 5444 (1957).

(31) N. F. Hall and M. R. Sprinkle, ibid., 54, 3469 (1932).

(32) Daugherty, op. cit., p. 20.

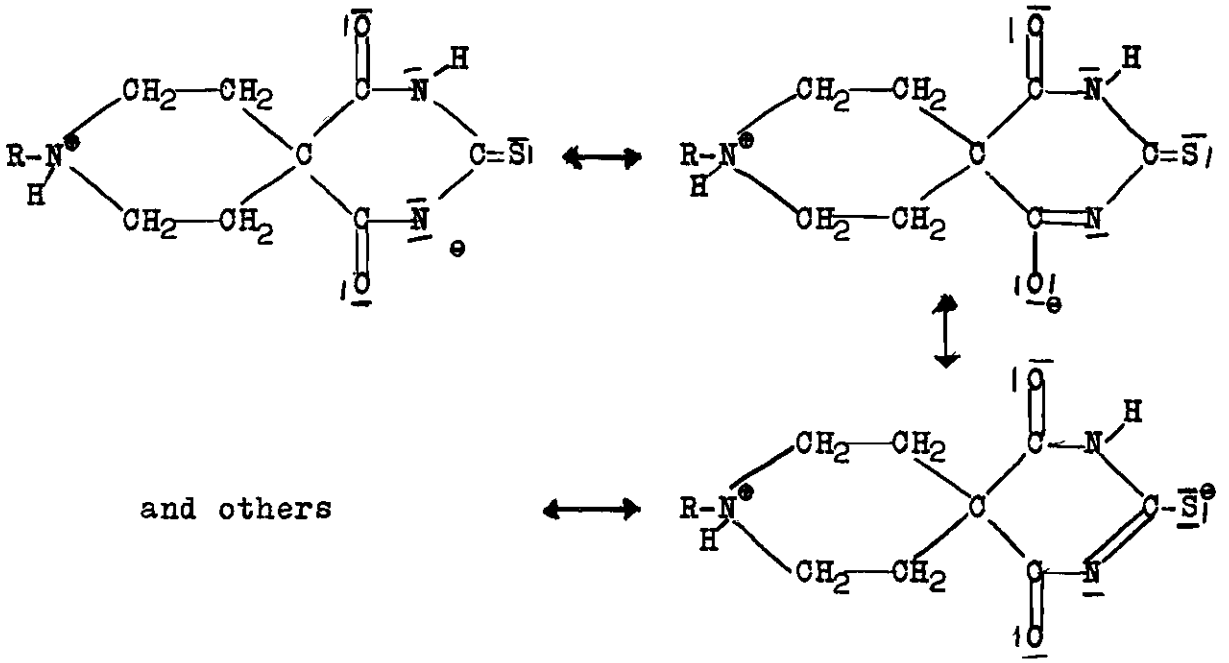


Figure 12. Resonance Structure of Spiropiperidine-4',5-(2-thiobarbituric) Acids

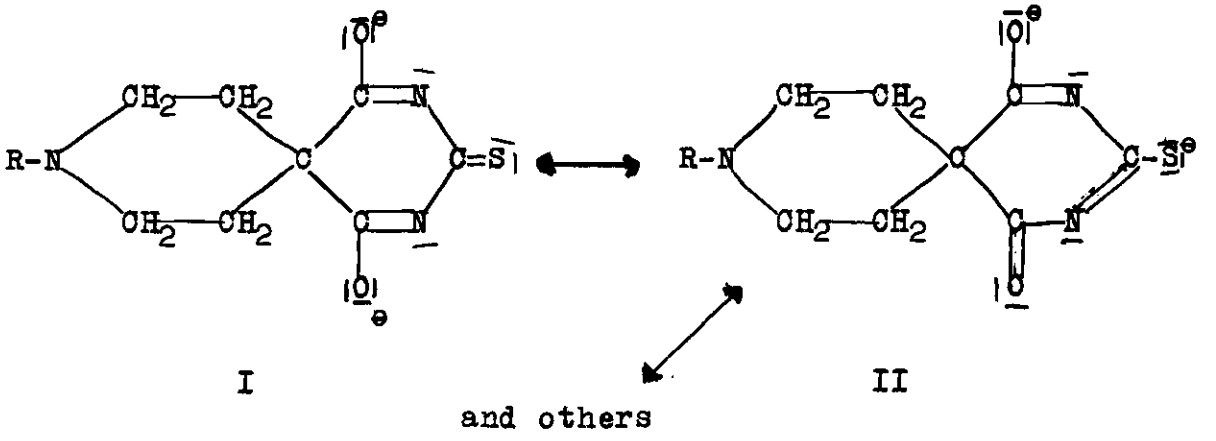


Figure 13. Spiro Divalent Ion

ran-4',5-(2-thiobarbituric) acid which was attributed to the dianionic species. Spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid and spiro-1'-m-tolylpiperidine-4',5-(2-thiobarbituric) acid showed no absorption bands when a saturated solution, in distilled water, was scanned in this region, while the 1'-alkyl compounds showed a band at 288 millimicrons. This band is probably due to the monoanion (salt) (Figure 12). A similiar shift to lower energy was observed in the spiropiperidine-4',5-barbituric acids and was explained as being due to steric strain introduced by the spiro ring (32). The strain probably decreases the contribution of a structure such as II in Figure 13.

The rapid decrease in the absorption of spiropiperidine-4',5-(2-thiobarbituric) acids is due to the hydrolysis of these compounds. In a single small scale experiment spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid was hydrolysed in about three minutes with one equivalent of sodium hydroxide to a compound which was identified as 1-phenylpiperidine-4-carbonylthioureide (Figure 14).

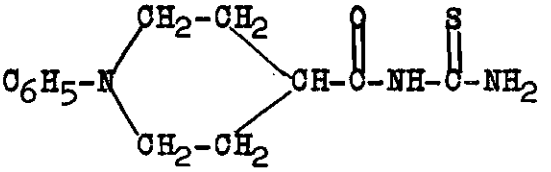
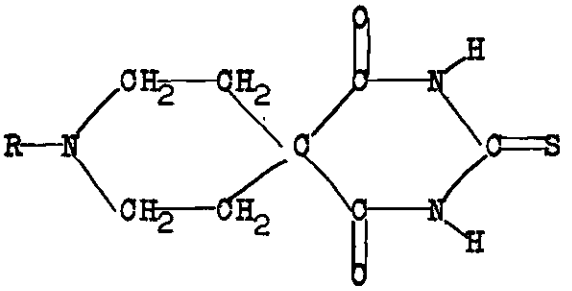


Figure 14. 1-Phenylpiperidine-4-carbonylthioureide

Table 2. Spiropiperidine-4',5-(2-thiobarbituric) Acids



R =	% Yield[1] (salt)	% Yield[2] (acid)	λ Max.[3] (mμ)	M.P.[4] (°C.)
Methyl	64	16	274	276-277
Ethyl	75	25	274	252-253
iso-Propyl	90	10	274	256-257
n-Butyl	86	16	274	216-217
Benzyl	90	16	274	253-255
2-Phenylethyl	86	36	275	213-214
Phenyl	84	93	276	223-224
m-Tolyl	88	93	274	235-236

[1]Per cent yield of salt (based on ester).

[2]Per cent yield of acid (based on salt).

[3]Ultraviolet absorption maximum in 1 N sodium hydroxide.

[4]Uncorrected (all decompose).

CHAPTER III

EXPERIMENTAL

All of the boiling points reported herein are uncorrected. The melting points are uncorrected and were determined in capillary tubes heated in an aluminum block. Elemental analyses were done by Galbraith Laboratories, Knoxville, Tennessee, or Clark Microanlytical Laboratories, Urbana, Illinois.

Synthesis via 5,5-bis(2-iodoethyl)-2-thiobarbituric Acid. (Procedure I)

Spirotetrahydropyran-4',5-(2-thiobarbituric) Acid.--The following is based on a procedure used by Daugherty (33).

A solution of sodium tert.-butoxide was prepared from 13.8 g. (0.63 g. atom) of sodium and 1200 ml. of tert.-butyl alcohol. First, 31.0 g. (0.41 mole) of thiourea and then 69.0 g. (0.30 mole) 4,4-dicarbethoxytetrahydropyran were added to the butoxide and the mixture refluxed with stirring for 24 hr. The reaction mixture was then divided into two 400-ml. portions and one 500-ml. portion. Dry hydrogen chloride gas was passed into one of the 400-ml. portions until it was acidic to moist litmus. After standing in a

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(33) Ibid., p. 83.

refrigerator for 48 hr. the crude product and sodium chloride were collected by suction filtration. The filter cake was broken up and washed thoroughly with cold water to remove sodium chloride. The spirotetrahydropyran-4',5-(2-thiobarbituric) acid was collected with suction, sucked dry, and recrystallized from iso-propyl alcohol. This gave 10.2 g. of pale yellow plates of m. p. 216-218° C. Assuming that four-thirteenths of the original mixture was used, this weight of product represents 54 per cent of the theoretical yield. After the second 400-ml. portion had been allowed to stand at room temperature for 24 hr., the acid was obtained from the salt in the manner just described. It weighed 11.2 g. which is 61 per cent of the theoretical yield (m. p. 216-218° C.). The third portion, 500-ml., of the reaction mixture was refluxed for 24 hr. longer and then worked up as before. It yielded 10.7 g. or 47 per cent of the theoretical yield.

Attempted preparation of 5,5-bis(2-iodoethyl)-2-thiobarbituric) Acid.--A mixture of 4.3 g. (0.02 mole) of spirotetrahydropyran-4',5-(2-thiobarbituric) acid, 13.5 g. (0.08 mole) of potassium iodide, and 30.5 g. of 95 per cent phosphoric acid was stirred and heated on an oil bath at 120° C. for five hours. As the reaction proceeded, large quantities of hydrogen sulfide were evolved and the mixture became black. The mixture was cooled and poured onto 200 g. of crushed ice whereupon a sticky mass resulted. The ice was allowed to melt

and the tar washed several times with cold water. After drying in a vacuum desiccator (water pump pressure) the tar was dissolved in 200 ml. of chloroform. When about two-thirds of the solvent was evaporated, 0.30 g. of brown crystals were deposited. Further evaporation gave only tarry material which was discarded. After a single recrystallization from chloroform the material melted (with decomposition) over a six degree range (149-155° C.). By sodium fusion, the material was shown to contain nitrogen, sulfur, and iodine. Since the material was consumed in the foregoing experiments and subsequent and further attempts to duplicate the preparation failed, procedure I for the preparation of spiropiperidine-4',5-(2-thiobarbituric) acid was abandoned in favor of another route.

Synthesis with bis(2-haloethyl)amines and bis(2-p-toluenesulfonyloxyethyl)amines (Procedure II)

This synthesis, outlined in Figure 10 (page 13), was unsuccessful for the preparation of spiro-1'-alkylpiperidine-4',5-(2-thiobarbituric) acid but was successful for two spiro-1'-arylpiperidine-4',5-(2-thiobarbituric) acids. In the synthesis of the latter compounds it was found advantageous to use bis(2-p-toluenesulfonyloxyethyl) aryl amines instead of bis(2-chloroethyl) aryl amines because of the difficulty of separation of the latter from the corresponding 1-aryl-4,4-dicarbethoxypiperidines.

Bis(2-chloroethyl)amine hydrochloride.--Two hundred grams (1.9 mole) of bis(2-hydroxyethyl)amine was dissolved in 400 ml. of chloroform contained in a 2000-ml. beaker. Dry hydrogen chloride gas was bubbled into the solution until there was a gain in weight of 69.5 g., (1.9 moles). After the addition of another 400-ml. portion of chloroform, 500 g. of thionyl chloride was added slowly with stirring. It was necessary to cool the reaction mixture by placing it in a pan of ice water, but the temperature could be held between 45 and 50° C. After all the thionyl chloride had been added the mixture became quite viscous and was yellow in color. An additional 400 ml. of chloroform was added and the temperature (45-50° C.) maintained for one hour with occasional stirring. The solid which had separated was collected with suction and washed three times with cold (0° C.) chloroform. It weighed 295 g. and had a melting point of 207-209° C. This amounted to 82 per cent of the theoretical yield.

Bis(2-chloroethyl)amine has been reported to decompose violently upon heating (34). Thus this salt was stored until ready for use and no attempt was made to obtain and to purify the free-base.

Attempted preparation of 4,4-dicarbethoxypiperidine.--For this compound two methods were used.

Method 1. Sodium ethoxide-ethanol.--This procedure is similar to that used by Harnest and Burger for the preparation of

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(34) Ibid., p. 33.

4,4-dicarbethoxytetrahydropyran from bis(2-chloroethyl) ether and diethyl malonate (15).

Sodium ethoxide was prepared by slowly adding 9.2 g. (0.4 g. atom) of sodium to 200 ml. of absolute alcohol contained in a 1000-ml. round-bottomed flask fitted with a Teflon blade stirrer and a reflux condenser. Thirty-four g. (0.2 mole) of diethyl malonate and bis(2-chloroethyl)amine (made by the treatment of 35.0 g. (0.2 mole) of the hydrochloride salt with excess 20 per cent sodium hydroxide solution and drying over potassium hydroxide pellets for 10 min.) were added to the ethoxide solution and then stirred while heating at the reflux temperature. The mixture became turbid (due to the formation of sodium chloride) almost as soon as the amine was added. After six hr. of refluxing and stirring, 4.6 g. (0.2 g. atom) of sodium dissolved in 100 ml. of absolute ethanol was added and refluxing was continued for 36 hr. At the end of this time, the sodium chloride was removed by suction filtration and the ethanol distilled off at atmospheric pressure. The brownish-orange liquid that remained was mixed with 100 ml. of water and extracted with three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate for 24 hr. and the ether removed by distillation at atmospheric pressure. Distillation of the residual oil at 7 mm. pressure yielded 30 g. of a liquid boiling at 74° C. A comparison of the infrared spectrum of this liquid with that of an authentic sample of diethyl mal-

onate showed the two to be the same. The temperature of the pot was taken up to 200° C. and the pressure was reduced to 1 mm. of mercury but no more material distilled. Some brown tarry material remained in the distillation pot.

Method 2. Sodium-toluene.--This is a modification of the procedure used by Anker et al. for the preparation of 1-phenyl-4,-4-dicarbethoxypiperidine from bis(2-chloroethyl) phenylamine and diethyl malonate (19).

In a 500-ml. three-necked round-bottomed flask equipped with a stirrer and reflux condenser were placed 43.0 g. (0.25 mole) of diethyl malonate and 200 ml. of dry toluene. Sic g. (0.25 mole) of sodium metal was added in small pieces so as to keep the reaction from becoming violent. The sodio-diethyl malonate-toluene mixture was heated to reflux and the bis(2-chloroethyl)amine from 35.0 g. (0.2 mole) of the hydrochloride salt[1] was added. A small amount of precipitate was formed immediately and increased as the mixture was refluxed and stirred for 24 hr. The mixture was allowed to cool to room temperature and was poured into 100 ml. of cold water. The resulting layers were separated and the aqueous layer extracted with two 50-ml. portions of toluene. The combined toluene extracts and the toluene layer were dried over calcium sulfate (Drierite) and the toluene removed by distillation. The oil that remained was vacuum distilled and 12.6 g. of

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[1] See above, page 29.

diethyl malonate was collected at 75°/7 mm. (Infrared spectrum). No other material could be distilled from the tarry residue even though the temperature of the distillation pot was allowed to reach 223° C. at a pressure of 3 mm. of mercury.

Bis(2-chloroethyl)phenylamine.--The following is an adaptation of a procedure used by Robinson and Watt (35). A solution of 100 g. (0.55 mole) of bis(2-hydroxyethyl)phenylamine in 200 ml. of chloroform was placed in a 1000-ml. three-necked flask fitted with a stirrer and reflux condenser. A gas absorption tube (splash trap) was affixed to the top of the condenser. The flask was placed in an ice bath and 120 g. (0.58 mole) of phosphorous pentachloride was added in small portions over a period of 45 min. Copious quantities of hydrogen chloride were evolved during this addition. The mixture was heated on a steam bath (ca. 80° C.) for six hours. The solution was then cooled to room temperature and washed three times with 100-ml. portions of water. After drying with calcium chloride the chloroform was removed by distillation. The product, bis(2-chloroethyl)phenylamine, was distilled through a heated eight-inch Vigreaux column, and had a b. p. 155-157°/6 mm. (lit. (35) 144°/4 mm.). The product, pale-yellow when freshly distilled but discoloring on standing, weighed

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(35) R. Robinson and J. Watt, J. Chem. Soc., 1536 (1939).

79.2 g. (66 per cent of theoretical). Duplication of the above procedure gave bis(2-chloroethyl)phenylamine in 48 per cent of theoretical yield.

1-Phenyl-4,4-dicarbethoxypiperidine.--The following is a modification of the procedure used by Anker et al. (21).

Diethyl malonate (61.0 g., 0.38 mole) was reacted with 9.0 g. (0.38 g. atom) of sodium in 300 ml. of toluene and then treated with 70.0 g. (0.38 mole) of bis(2-chloroethyl)phenylamine. The mixture was refluxed for 24 hr. and worked up as in the attempted preparation of 4,4-dicarbethoxypiperidine[1]. Fractionation of the reaction mixture yielded: 18.5 g. of diethyl malonate, b. p. 52°/1 mm.; 49.9 g. of bis(2-chloroethyl)phenylamine, b. p. 118-126°/.5-1 mm; and 3.3 g. of 1-phenyl-4,4-dicarbethoxypiperidine, b. p. 155-158°/1-2 mm. This is 95 per cent based on the bis(2-chloroethyl)phenylamine reacted but the product was contaminated with some of the starting material (shown by chloride test after sodium fusion) thus the following procedure, using bis(2-p-toluenesulfonyloxyethyl)phenylamine, was used for the preparation of 1-phenyl-4,4-dicarbethoxypiperidine.

Preparation of bis(2-p-toluenesulfonyloxyethyl)phenylamine.--The following is a modification of a procedure used by Starnes (36).

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[1]See above, page 30.

(36) Starnes, op. cit., p. 64.

Into a 1000-ml. three-necked flask fitted with a Teflon stirrer and a thermometer were placed 45.0 g. (0.3 mole) of bis(2-hydroxyethyl)phenylamine and 300 ml. of anhydrous pyridine. The solution was cooled to 5° with an ice-salt bath and 120 g. (0.63 mole) of p-toluenesulfonyl chloride was added at at such a rate that the temperature could be maintained at 12° or less; about one hour was required for the addition. The mixture, which had turned brown during the addition of the p-toluenesulfonyl chloride, began to thicken due to the formation of a pale-yellow precipitate. After stirring at 5-6° for 45 min., the mass was poured into a mixture of 400 g. of crushed ice and 400 ml. of water. Concentrated ammonium hydroxide was added until the mixture was basic. The beaker containing the mixture was placed in an ice bath and the contents stirred whereupon the product began to form in oily lumps which soon solidified. The mixture was kept in the ice bath until the crude product was collected by suction filtration. The filter cake was pressed between sheets of absorbent paper, broken into small pieces, and placed in a vacuum desiccator (water pump pressure) for 12 hr. to remove residual pyridine and water. Recrystallization was accomplished by dissolving the crude material in 1000 ml. of boiling absolute ethanol and adding 1000 ml. of n-hexane. The bis(2-p-toluenesulfonyloxyethyl)phenylamine, 72.0 g., was deposited as pale greenish-yellow crystals upon cooling in an ice bath and had a m. p. of 89-90°. This was 49 per cent of the theoretical yield.

On subsequent runs of this reaction it was found that the yield could be improved considerably if the crude material was purified by dissolving it in hot acetone followed by addition of water to the cloud point. The container was then placed in an ice bath; pale yellow crystals of product formed as the solution was stirred rapidly. About 2.5 ml. of acetone per gram of crude bis(2-p-toluenesulfonyloxyethyl)phenylamine was used. Yields of 74 and 80 per cent were obtained on duplicate runs using this purification procedure.

1-Phenyl-4,4-dicarbethoxypiperidine (37).--In a typical experiment, 93.5 g. (0.58 mole) of diethyl malonate and 500 ml. of anhydrous toluene were placed in a 2000-ml. three-necked flask equipped with a reflux condenser and stirrer. Seven grams (0.3 g. atom) of sodium was added in small pieces. As the sodium "dissolved" the solution became pale yellow but appeared to be one phase. While stirring vigorously, 69.0 g. (0.14 mole) of bis(2-p-toluenesulfonyloxyethyl)phenylamine was added through a powder funnel. Much frothing accompanied the addition. The mixture became cloudy and finally quite thick, probably due to the formation of sodium p-toluenesulfonate. Refluxing and stirring were continued for 24 hr. and then the contents of the flask were cooled to room temperature and poured into one liter of cold water. The toluene phase was removed, combined with two 50-ml. toluene extracts of the water

(37) Starnes, op. cit., p. 66.

phase, and dried over white Drierite for 24 hours. Once indicating Drierite was used and the solution became green; however, this had little effect on the results. The toluene was removed at atmospheric pressure and the residual yellow oil fractionated through an 8-inch Vigreaux column under reduced pressure. A fore-run of diethyl malonate, b. p. 50-55°/3 mm., and 1-phenyl-4,4-dicarbethoxypiperidine, b. p. 158-160°/3 mm. were collected. The latter compound, a pale oil which solidified on standing, weighed 34.4 g. (80 per cent of theoretical yield). The product crystallized from methanol in white prisms, m. p. 52-53° (lit. (21) 53°). The infrared spectrum was identical to an authentic sample of this compound[1].

Preparation of Spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid. Method 1.--Sodium ethoxide was prepared by adding 1.40 g. (0.06 g. atom) of sodium to 100 ml. of absolute ethanol in a 200-ml. three-necked flask fitted with a stirrer and reflux condenser. The system was protected from atmospheric moisture by a drying tube filled with calcium chloride which was affixed to the top of the condenser. Three grams (0.04 mole) of thiourea was added. When this had dissolved, 6.10 g. (.02 mole) of 1-phenyl-4,4-dicarbethoxypiperidine was added. The contents of the flask were stirred with boiling under reflux for 12 hr. during which time a cloudiness appeared. Upon cooling to about 0°, a heavy, pale yellow precipitate

[1] This material was supplied by W. H. Starnes.

formed in the flask. A few drops of methyl red was added and dry hydrogen chloride passed in until the solution became pink. The crude product along with sodium chloride was collected by suction filtration, washed with cold water until chloride-free, and dried in a vacuum desiccator. The crude product was crystallized by dissolving in hot acetone, adding water to the cloud point, and allowing to cool. As the solution cooled and the acetone slowly evaporated, spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid crystallized in small yellow crystals; 3.1 g. of purified product was obtained representing a 54 per cent yield. The material melted at 223.5-224.5° with decomposition. An ultra-violet spectrum of this compound in 1 N sodium hydroxide showed an absorption band at 276 millimicrons. The infrared spectrum is reproduced in Figure 15. Analysis indicated the sample to be a mono-hydrate.

Analysis Calculated for $C_{14}H_{15}N_3O_2S \cdot H_2O$: C, 54.70; H, 5.57; N, 13.67; S, 10.43; Found: C, 55.00; H, 5.30; N, 13.86; S, 10.54.

Method 2.--In a subsequent experiment the same quantities of materials were reacted as above except 75 ml. instead of 100 ml. of absolute alcohol was used. The reaction was carried out in a 125-ml. Erlenmeyer flask with a condenser attached. The mixture was stirred and heated on a Gyrotherm[1]. After

[1] Trademark of Will Corporation for a magnetic stirrer-heater combination.

24 hr. of stirring under reflux the contents of the flask were cooled to 0° C. and filtered. Disodium spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric), 5.4 g., was collected and dried in a vacuum desiccator; this was 84 per cent of theoretical. Ten millimoles, 3.23 g., was stirred with 40 g. of dry Amberlite IRC-50[1] ion exchange resin in 100 ml. of absolute ethanol for 24 hr. The resin-alcohol slurry was heated until the alcohol began to boil and then was filtered. After washing the resin with two 50-ml. portions of boiling ethanol, evaporation of the ethanol from the combined extracts and washes left 2.7 g. of a pale yellow solid, the spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid of m. p. 223-224°. This represents a 93 per cent yield in the acidification step, or overall 78 per cent of the acid based on 1-phenyl-4,4-dicarbethoxypiperidine. This sample of acid had an absorbtion band at 276 millimicrons in 1 N sodium hydroxide.

Bis(2-p-toluenesulfonyloxyethyl)-m-tolylamine.--The following is an adaptation of a procedure used by Starnes (38).

Into a 3000-ml. three-necked flask equipped with a stirrer and a thermometer was placed 195 g. (1 mole) of bis(2-hydroxyethyl)-m-tolylamine and 1200 ml. of dry pyridine. The solution was cooled to 5° in an ice bath and 400 g. (2.1 mole) of p-toluenesulfonyl chloride was added at such a

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[1]Rohm and Haas Co. carboxylic acid resin.

(38) Starnes, op. cit., p. 70.

rate that the temperature was held at about 12°. Toward the end of the addition, some yellow crystals began to form in the solution. Stirring at 5-12° was continued for one hr. Equal portions of the contents of the flask were then poured into two 4000-ml. flasks each containing 1000 g. of ice and 1000 ml. of water. The solutions were made basic with ammonium hydroxide whereupon the product started to precipitate as a pasty mass which soon hardened. The combined solids from the two portions were washed by decantation several times with 1000-ml. portions of cold water. Finally the solid was collected, dried by pressing between pieces of paper towel, and placed in a vacuum desiccator for 12 hr. The crude bis(2-*p*-toluenesulfonyloxyethyl)*m*-tolylamine was purified by dissolving it in 1000-ml. of boiling acetone, adding water to the cloud point, and cooling in an ice bath. While cooling, the solution was stirred vigorously and the product crystallized as a pale yellow solid. The product (m. p. 82-84°) weighed 432 g., or 86 per cent of theoretical. Although the product melted a little lower than reported (*cf.* Starnes' value 86-87° (37)) it was used without further purification for the subsequent preparation of 1-*m*-tolyl-4,4-dicarbethoxypiperidine.

1-*m*-tolyl-4,4-dicarbethoxypiperidine.--This material was prepared by the method of Starnes (39) on a 0.58 mole scale with a yield of 76 per cent.

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(39) Starnes, *op. cit.*, p. 72.

Spiro-1'-*m*-tolylpiperidine-4',5-(2-thiobarbituric) acid.--A 125-ml. Erlenmeyer flask with a standard taper joint was fitted with a condenser which had a drying tube to protect the system from atmospheric moisture. A Teflon coated magnetic stirring bar was put into the flask along with 50 ml. of absolute alcohol. Two grams (0.09 g. atom) of sodium was added, and when the sodium had dissolved, 4.57 g. (0.06 mole) of thiourea and 9.47 (0.03 mole) of 1-*m*-tolyl-4,4-dicarbethoxypiperidine were added. The mixture was placed on a Gyrotherm and refluxed with stirring for 14 hr. During this time the solution became cloudy. Upon cooling disodium spiro-1'-*m*-tolylpiperidine-4',5-(2-thiobarbiturate) precipitated. The salt was collected with suction, washed with two two-ml. portions of cold absolute ethanol, and finally washed with 20 ml. of dry diethyl ether. After the salt was dried in a vacuum desiccator for 10 hr. it weighed 9.23 g. or 88 per cent of the theoretical yield.

Acidification of 3.47 g. (0.01 mole) of disodium spiro-1'-*m*-tolylpiperidine-4',5-(2-thiobarbiturate) was accomplished by stirring with 30 g. of dry Amberlite IRC-50 ion exchange resin in 100 ml. of absolute alcohol for 24 hr. The free acid, 2.8 g., was obtained by heating the alcohol-resin mixture, filtering, and evaporating the alcohol. This weight of acid was 93 per cent of the theoretical yield. An analytical sample was prepared by recrystallization from ethanol three times, m. p. 235-6°. The infrared spectrum is

shown in Figure 16. The ultra-violet spectrum in 1 N sodium hydroxide showed an absorption band at 274 millimicrons which decreased rapidly.

Analysis Calculated for $C_{15}H_{17}N_3O_2S$: C, 59.39; H, 5.65; N, 13.85; S, 10.58; Found: C, 59.79; H, 5.51; N, 13.70; S, 10.45.

Synthesis via 1-Alkyl-4-carbethoxypiperidines (Procedure III)

This route to 1-alkyl-4,4-dicarbethoxypiperidines and thus to spiro-1'-alkylpiperidine-4',5-(2-thiobarbituric) acids is diagrammed in Figure 11, page 16.

Ethyl isonicotinate (4-carbethoxypyridine).--The following is a procedure similar to that used by Pailer et al. (22).

A 3000-ml. flask was fitted with a large Soxhlet extractor. Into the flask was put 123 g. (1 mole) of isonicotinic acid, 460 g. (10 mole) of absolute ethanol, and 720 ml. of benzene. These materials were mixed and then 117.6 g. (1.2 mole) of sulfuric acid was added slowly with swirling; the mixture became warm and turned pale amber in color - some isonicotinic acid was undissolved. The mixture was refluxed with 200 g. of anhydrous magnesium sulfate in the cup of the extractor. After about one hour the solid had completely dissolved, whereupon refluxing was continued for 36 hr. After cooling, first to room temperature and then in an ice bath, the mixture was poured into a mixture of 400 g. of water and 400 g. of crushed ice contained in a 4000-ml. beaker which in turn was sitting in an ice bath. Solid sodium carbonate was

added until the aqueous phase was basic towards litmus. After the ice in the mixture had melted, the heterogeneous mixture was transferred to a 4000-ml. separatory funnel and allowed to warm until the benzene layer thawed. The two layers were separated, the water layer extracted twice with 100-ml. portions of benzene, and the combined extracts dried with anhydrous magnesium sulfate for 18 hr. The benzene was removed using a Rotovap on a steam bath. Distillation of the residual oil through an 8-inch Vigreaux column yielded 119 g. of ethyl isonicotinate, b. p. 74-76°/2 mm. This is a 75 per cent yield; however, on other runs yields of 86 and 92 per cent were obtained.

Preparation of 1-methyl-4-carbethoxypyridinium iodide.--The following is a modification of a procedure used by Krapcho (23).

The following were refluxed together for six hr. in a 500-ml. flask: 67.6 g. (0.44 mole) of ethyl isonicotinate, 100 g. (0.70 mole) of methyl iodide, and 180 ml. of absolute alcohol. The pale orange color which developed when these materials were mixed became darker upon refluxing. At the conclusion of the reflux period, the volatile materials were removed on a Rotovap leaving an orange solid which was dissolved in 180 ml. of hot absolute ethanol. Diethyl ether was added until the solution became cloudy. The flask containing the solution was refrigerated for 12 hr. The orange, 1-methyl-4-carbethoxypyridinium iodide was collected with suction

and dried in a vacuum desiccator (124 g. or 96 per cent of theoretical yield). Since the salt was very hygroscopic it was decided to use it in the preparation of 1-methyl-4-carbethoxypiperidine without further purification or characterization.

Preparation of 1-methyl-4-carbethoxypiperidine.--Twenty grams (0.068 moles) of 1-methyl-4-carbethoxypyridinium iodide was placed in a 500 ml. Parr hydrogenation bottle along with 150 ml. of absolute ethanol. The catalyst, 0.5 g. of platinum dioxide, was added and the contents of the bottle shaken in an atmosphere of hydrogen until the theoretical amount of hydrogen, as measured by the pressure drop in the system, had been absorbed. The catalyst was removed by filtration and the ethanol by evaporation (Rotovap) leaving a pale-yellow solid. The hydrogenated salt from six such runs was dissolved in 400 ml. of cold water. While cooling the solution in an ice bath, solid sodium carbonate was added until the solution was basic to litmus at which time the product separated as a brown oil. The product was removed and the water phase extracted with two 100-ml. portions of ether. After drying with Drierite, the ether was removed by distillation. Fractionation of the oil through an 8-inch Vigreaux column yielded 23 g. of 1-methyl-4-carbethoxypiperidine, b. p. 58-60°/2 mm. (lit. (23) b. p. 58-59°/2 mm.). Although this is only a 32 per cent yield, a 48 per cent yield was also realized using the same procedure.

Purification of triphenyl carbinol.--Triphenyl carbinol which was prepared by the procedure of Adams and Johnson[1] (40) was purified by recrystallization from carbon tetrachloride. Four ml. of solvent per gram of crude carbinol was used.

Triphenylchloromethane.--This material was prepared by the method of Bachmann (41) from acetyl chloride and triphenylcarbinol. The material was stored in a jar in an evacuated desiccator until ready for use.

Triphenylmethylsodium.--Triphenylmethylsodium in diethyl ether was made from triphenylchloromethane and sodium amalgam by the method of Renfrow and Hauser, and standardized by their procedure (42).

1-Methyl-4,4-dicarbethoxypiperidine.--A 2000-ml. graduated bottle was fitted with an inlet tube and a pressure-equalizing dropping funnel. The inlet tube was connected to the bottle of triphenylmethylsodium by polyethylene tubing. The bottle and funnel were flushed with dry nitrogen, a Teflon coated magnetic stirring bar was placed in the bottle, and 947 ml.

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[1] This compound was prepared as a part of an undergraduate organic laboratory course.

(40) R. Adams and J. R. Johnson, Laboratory Experiments in Organic Chemistry, 4th Ed., The Macmillan Co., New York, N. Y., 1949, p. 393.

(41) W. Bachmann, in Organic Syntheses, Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 841.

(42) W. Renfrow and C. Hauser, ibid., Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 607.

of 0.123 N triphenylmethylsodium in ether was forced into the bottle with dry nitrogen. Over a period of 15 min., 21.0 g. (0.123 mole) of 1-methyl-4-carbethoxypiperidine in 25 ml. of dry diethyl ether was added through the dropping funnel. Even after stirring the mixture for one hour, the red color of the triphenylmethyl still persisted. An ether solution of 13.7 g. (0.139 mole) of ethyl chloroformate in 25 ml. of dry diethyl ether was then added slowly. The reaction was exothermic but the temperature did not reach the boiling point of ether. A white solid, sodium chloride, began to form immediately. Stirring was continued for 18 hr. after which the crude reaction mixture was poured into a separatory funnel containing 100 ml. of water. The two layers which formed were separated and the water layer was discarded, while the ether layer was extracted with 20 ml. of concentrated hydrochloric acid and 75 ml. of water. This time the ether layer was discarded after further extracting with two 25-ml. portions of water. The acid solution of 1-methyl-4,4-dicarbethoxypiperidine was cooled in an ice bath and when cold, was made basic with a sold solution of sodium hydroxide (100 ml. of 20 per cent was used). The oil which separated was removed and the aqueous phase extracted with four 100-ml. portions of diethyl ether. The combined ether extracts and oil layer were dried over Drierite for 12 hours. Removal of the ether by distillation and fractionation of the oil yielded 14.5 g. of 1-methyl-4,4-dicarbethoxypiperidine, b. p. 86-89°/2 mm.; methyl iodide salt, m. p. 146-148°;

and picrate, m. p. 123-124°. Schmutz (43) prepared the same compound by the hydrogenolysis of 1-benzyl-1-methyl-4,4-dicarbethoxypiperidine and reports, b. p. 134-137°/12 mm; methyl iodide salt, m. p. 148-9° and picrate, m. p. 123-125°.

Although the preceding represents a 49 per cent of theoretical, on a duplicate run a 53 per cent yield was realized.

Spiro-1'-methylpiperidine-4',5-barbituric acid.--Although it was not within the scope of this research to prepare barbituric acids, this compound was prepared as a "derivative" of the diester and at the same time, it was thought, to verify the synthesis by the method of Daugherty[1].

The disodium salt of spiro-1'-methylpiperidine-4',5-barbituric acid was prepared in 90 per cent yield on a 0.01 mole scale by the procedure described above[2]. Thus, 2.43 g. (0.01 mole) of 1-methyl-4,4-dicarbethoxypiperidine and 1.20 g. (0.02 mole of urea were allowed to react in the presence of sodium ethoxide (0.03 mole) in ethanol. After cooling, filtration of the mixture afforded 2.3 g. of the salt. Acidification of 1.28 g. (0.005 mole) of disodium spiro-1'-methylpiperidine-4',5-barbiturate with 1.1 g. (11 milliequivalents) of dry Amberlite IRC-50 ion exchange resin in ethanol yielded

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[1]See above, page 7.

[2]See above, page 39.

(43) J. Schmutz, F. Kunzle, and R. Hirt, Helv. Chim. Acta, 37, 1762 (1954).

0.51 g. of spiro-1'-methylpiperidine-4',5-barbituric acid (48 per cent). An analytical sample prepared by three crystallizations from absolute ethanol melted at 281-282° with decomposition. Daugherty (44) reports 164-166°.

Analysis Calculated for $C_9H_{13}N_3O_3$: C, 51.21; H, 6.20; N, 19.90; Found: C, 51.20; H, 5.87; N, 19.88.

The ultraviolet spectrum in distilled water shows an absorption maximum at 240 millimicrons which decreases rapidly. This band is attributed to absorption by a monoanionic specie[1].

Spiro-1'-methylpiperidine-4',5-(2-thiobarbituric) acid.--Condensation of 9.0 g. (0.037 moles) of 1-methyl-4,4-dicarbethoxypiperidine with 5.63 g. (0.074 mole) of thiourea by the method used for the preparation of spiro-1'-m-tolylpiperidine-4',5-(2-thiobarbituric) acid[2] yielded 6.1 g. (64 per cent) of disodium spiro-1'-methylpiperidine-4',5-(2-thiobarbiturate). A 16 per cent yield was obtained in acidification of the salt with one equivalent of resin, extraction of the resin with ethanol in a Soxhlet extractor did not improve the recovery. An analytical sample, prepared by three recrystallizations from absolute ethanol, had a m. p. of 276-277°.

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[1]For a discussion of the ultraviolet spectra of barbituric acids see ref. (11) p. 19 and references cited therein.

[2]See above, page 39.

(44) Daugherty, op. cit., p. 64.

Analysis Calculated for $C_9H_{13}N_3SO_2$: C, 47.56; H, 5.77; N, 18.48; S, 14.10; Found: C, 47.93; H, 5.83; N, 17.98; S, 13.82.

The infrared spectrum is shown in Figure 17. The compound had a characteristic ultraviolet spectrum, i.e. strong band at 274 millimicrons in 1 N sodium hydroxide.

1-Ethyl-4-carbethoxypyridinium iodide.--Ethyl iodide, 78.0 g. (0.5 mole), and ethyl isonicotinate, 60.4 g. (0.4 mole), were allowed to react in ethanol by the procedure for the preparation of 1-methyl-4-carbethoxypyridinium iodide[1]. The crude salt, a deep orange solid, weighed 113.0 g. (92 per cent). The material was very hygroscopic and difficult to purify. Thus even after three recrystallizations samples of the compound still poisoned the platinum catalyst so rapidly it was not possible to hydrogenate the material. Use of the compound for subsequent experiments was therefore not possible.

1-Ethyl-4-carbethoxypyridinium bromide.--Using the procedure described earlier[2], ethyl bromide (1.20 mole) and ethyl isonicotinate (1.0 mole) were allowed to react to yield 1-ethyl-4-carbethoxypyridinium bromide (95 per cent of theoretical). After a single recrystallization from alcohol-ether this compound could be hydrogenated and was suitable for use in subsequent experiments.

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[1] See above, page 41.

[2] See above, page 41.

1-Ethyl-4-carbethoxypiperidine.--Hydrogenation of 96.7 g. (0.37 mole) of 1-ethyl-4-carbethoxypyridinium bromide and subsequent work up[1] afforded 43.7 g. of 1-ethyl-4-carbethoxypiperidine, b. p. 74°/0.5 mm. This is 61 per cent of theoretical yield. The compound showed strong carbonyl absorption at 5.74 microns (Figure 18.). Vapor phase chromatographic analysis indicated that there was only one component present. The material was used in the carbethoxylation reaction without further purification or characterization.

1-Ethyl-4,4-dicarbethoxypiperidine.--1-Ethyl-4-carbethoxypiperidine was carbethoxylated at the 4-position with triphenylmethylsodium using the same technique and ratios of reactants as described for the preparation of 1-methyl-4,4-dicarbethoxypiperidine[2]. The product[3] was fractionated through an 8-inch Vigreaux column and boiled at 91°/0.4 mm. The melting point of the methyl iodide salt was 152-153°. The same compound, 1-methyl-1-ethyl-4,4-dicarbethoxypiperidinium iodide, made by the reaction of 1-methyl-4,4-dicarbethoxypiperidine with ethyl iodide, melted at 151-152°; a 50-50 mixture of the two melted at 152-153°. The infrared spectrum is shown in Figure 19.

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[1] See above preparation of 1-methyl-4-carbethoxypiperidine.

[2] See above, page 43.

[3] Since the reaction mixture was spilled and the reaction was not repeated, no attempt to calculate yield was made.

Spiro-1'-ethylpiperidine-4',5-(2-thiobarbituric) acid.--The disodium salt was available from 1-ethyl-4,4-dicarbethoxypiperidine and thiourea by the same technique and using the same molar ratio of reactants described earlier[1]. Acidification of 2.85 g. (0.005 mole) of the salt with 2.0 g. of Amberlite IRC-50 ion exchange resin, followed by extraction (Soxhlet extractor) with ethanol for 24 hr. and evaporation of the alcohol yielded 0.60 g. (25 per cent) of spiropiperidine-4',5-(2--thiobarbituric) acid. An analytical sample was prepared by three recrystallizations from absolute ethanol, and had a m. p. of 252-253° (dec.).

Analysis Calculated for $C_{10}H_{15}N_3SO_2$: C, 49.77; H, 6.27; N, 17.41; S, 13.29; Found: C, 49.85; H, 6.13; N, 17.28; S, 12.89.

The infrared spectrum is shown in Figure 20. The ultraviolet spectrum shows a strong band at 274 millimicrons which decreases rapidly.

1-n-Butyl-4-carbethoxypyridinium bromide.--1-n-Butyl-4-carbethoxypyridinium bromide was prepared in 92 per cent yield by the reaction of n-butyl bromide with ethyl isonicotinate[2]. Since the material was to be used immediately and was hygroscopic, it was recrystallized only once and used with further characterization.

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[1] See above, page 39.

[2] The experimental detail is the same as that described earlier, page 41.

1-n-Butyl-4-carbethoxypiperidine.--1-n-Butyl-4-carbethoxypyridinium bromide afforded 1-n-butyl-4-carbethoxypiperidine in 73 per cent yield by catalytic hydrogenation[1]. The compound boiled at 94-96°/2 mm. The infrared spectrum showed a carbonyl band at 5.74 (Figure 21). Vapor phase chromatographic analysis indicated there was only one component present.

1-n-Butyl-4,4-dicarbethoxypiperidine.--This compound was synthesized in 72 per cent yield by carbethoxylation of 1-n-butyl-4-carbethoxypiperidine with ethyl chloroformate and triphenylmethylsodium[2]. The compound boiled at 113-114°/0.1 mm. and has a carbonyl absorption band at 5.74 microns (see Figure 22). The methyl iodide salt melted at 150-151° whereas the salt prepared from 1-methyl-4,4-dicarbethoxypiperidine and n-butyl iodide melted at 153-154°. A mixture of the two melted at 151-152°.

Spiro-1'-n-butylpiperidine-4',5-(2-thiobarbituric) acid.--Condensation of 1-n-butyl-4,4-dicarbethoxypiperidine with thiourea in the presence of sodium ethoxide yielded the disodium salt of spiro-1'-n-butylpiperidine-4',5-(2-thiobarbituric) acid in 86 per cent of theoretical yield[3]. Acidification of the salt with Amberlite IRC-50 in ethanol and subsequent extraction afforded spiro-1'-n-butylpiperidine-4',5-(2-thio-

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[1] See above, page 42.

[2] See above, page 43.

[3] For details and ratios of reactant, see above page 39.

barbituric) acid in 16 per cent yield. An analytical sample was prepared by three recrystallizations from absolute ethanol, and had a m. p. of 216-217° (dec.).

Analysis Calculated for $C_{12}H_{19}N_3SO_2$: C, 53.58; H, 7.11; N, 15.60; S, 11.90; Found: C, 53.58; H, 6.87; N, 15.19; S, 11.58.

The infrared spectra is shown in Figure 23. In 1 N sodium hydroxide the compound had an absorption maximum at 274 millimicrons.

1-iso-Propyl-4-carbethoxypyridinium bromide.--This compound, a white solid, was prepared from ethyl isonicotinate and 2-bromopropane in 69 per cent of theoretical yield[1]. It was recrystallized once from alcohol-ether and then used in a subsequent reaction.

1-iso-Propyl-4-carbethoxypiperidine.--Hydrogenation of 1-iso-propyl-4-carbethoxypyridinium bromide afforded 1-iso-propyl-4-carbethoxypiperidine in 61 per cent yield[2]. The material, a colorless oil, boiled at 81-84°/0.3 mm. The infrared spectrum showed a carbonyl absorption band at 5.74 microns (Figure 24). Vapor phase chromatographic analysis indicated only one component was present hence the material was used directly in the preparation of 1-iso-propyl-4,4-dicarbethoxypiperidine.

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[1] See above, page 41 for details.

[2] See above, page 42 for details.

1-iso-Propyl-4,4-dicarbethoxypiperidine.--Using triphenylmethylsodium and ethyl chloroformate, 1-iso-propyl-4-carbethoxypiperidine was carbethoxylated[1] to 1-iso-propyl-4,4-dicarbethoxypiperidine in 51 per cent yield. This diester boiled at 103-105°/0.1 mm. and showed a carbonyl absorption at 5.75 microns (Figure 25). Vapor phase chromatography indicated only one component. This material was used in the preparation of spiro-1'-iso-propylpiperidine-4',5-(2-thiobarbituric) acid. The methyl iodide salt of the diester melted at 162-164°. No salt could be obtained when 1-methyl-4,4-dicarbethoxypiperidine was reacted with iso-propyl iodide in ethanol solvent or without solvent.

Spiro-1'-iso-propylpiperidine-4',5-(2-thiobarbituric) acid.--The sodium salt of this acid was prepared in 90 per cent yield[2] but conversion to the acid was poor being, only 10 per cent. An analytical sample was prepared by several recrystallization from ethanol, m. p. 256-257° C (dec.).

Analysis Calculated for $C_{11}H_{17}N_3SO_2$: C, 51.74; H, 6.71; N, 16.43; S, 12.56; Found: C, 51.32; H, 7.01;

This compound showed the characteristic ultraviolet band at 274 millimicrons in 1 N sodium hydroxide solution.

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[1] See above, page 43.

[2] See above, page 39.

1-Benzyl-4-carbethoxypyridinium chloride.--This material was prepared in the usual manner[1] from benzyl chloride and ethyl isonicotinate. The yield of crude material was 90 per cent of theoretical. After a single recrystallization the salt was readily hydrogenated.

1-Benzyl-4-carbethoxypiperidine.--The preceding product was hydrogenated to 1-benzyl-4-carbethoxypiperidine in 65 per cent of theoretical yield[2]. The compound boiled at 126-128°/0.1 mm. and its infrared spectrum showed a carbonyl band at 5.74 microns (Figure 26).

1-Benzyl-4,4-dicarbethoxypiperidine.--By carbethoxylation[3] of 1-benzyl-4-carbethoxypiperidine, 1-benzyl-4,4-dicarbethoxypiperidine was obtained in 72 per cent yield. It was a colorless liquid having a b. p. 165-167°/0.2 mm. The characteristic carbonyl absorption band at 5.75 (Figure 27) microns was observed. The salt made by the reaction of this compound with methyl bromide melted at 174-176°; Schmutz et al. (41) reported the same compound (made by a different route) to melt at 176°.

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[1]See above, page 41.

[2]See above, page 42.

[3]See above, page 43.

Spiro-1'-benzylpiperidine-4',5-(2-thiobarbituric) acid.--The disodium salt was prepared in the usual manner[1] in 90 per cent yield. Acidification with ion exchange[2] resin afforded the acid in 16 per cent yield. An analytical sample was prepared by three recrystallizations from absolute ethanol, m. p. 253-255° (dec.).

Analysis Calculated for $C_{15}H_{17}N_3SO_2$: C, 59.39; H, 5.65; N, 13.85; S, 10.57; Found: C, 59.11; H, 5.57; N, 14.17; S, 10.19.

The infrared spectrum of this compound is given in Figure 28. The ultraviolet spectrum showed a band at 274 millimicrons.

β-Phenylethyl chloride.--β-Phenylethyl chloride was prepared from β-phenylethyl alcohol and thionyl chloride by the method of Ward (45).

Attempted preparation of 1-(2-phenylethyl)-4-carbethoxypyridinium chloride.--Into a 200-ml. flask fitted with a reflux condenser were placed 40 g. (0.25 mole) of ethyl isonicotinate, 39 g. (0.28 mole) of 2-phenylethyl chloride, and 100 ml. of absolute ethanol. The solution was refluxed for 24 hr. and then the alcohol was removed using a Rotovap (steam bath) leaving a colorless oil. The oil was dissolved in about 1000 ml. of anhydrous ether and the solution placed in a refrigera-

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[1] See above, page 39.

[2] See above, page 39.

(45) A. Ward, J. Chem. Soc., 445 (1927).

tor. After three days no solid was present in the flask; if the salt had been formed it was felt that it should be insoluble in ether. This approach to 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine was discontinued at this time in favor of another synthesis of this compound.

1-(2-Phenylethyl)-4,4-dicarbethoxypiperidine.--The following is based on a procedure developed in these laboratories by J. G. Thweatt (46). 4,4-Dicarbethoxypiperidine[1], 20.6 g. (0.09 mole); phenylacetaldehyde, 12.0 g. (0.1 mole); platinum dioxide, 0.5 g.; and absolute ethanol, 75 ml. were put into a reaction bottle and hydrogenated on the Parr apparatus. After the compound had absorbed the theoretical amount of hydrogen, the reaction was discontinued. The catalyst was filtered from the reaction mixture and then the alcohol was removed on a Rotovap (steam bath). Fractionation of the residual oil yielded 23.4 g. (78 per cent of theoretical) of 1-(2-phenylethyl)-4,4-dicarbethoxypiperidine having a b. p. of 162-163°/0.1 mm. The infrared spectrum of this material was identical to that of an authentic sample of the diester[1].

Spiro-1'-(2-phenylethyl)-4',5-(2-thiobarbituric) acid.--1-(2-Phenylethyl)-4,4-dicarbethoxypiperidine was condensed with thiourea[2] to give the corresponding thiobarbiturate salt

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[1] This material was supplied by J. G. Thweatt.

[2] See above, page 39, for ratio of reactants and details.

(46) J. G. Thweatt, private communication.

in 86 per cent yield. This was acidified in the usual way to give a 36 per cent yield of the free acid. An analytical sample prepared by three crystallizations from ethanol was found to melt at 213-214°.

Analysis Calculated for $C_{16}H_{19}N_3SO_2$: C, 60.54; H, 6.03; N, 13.24; S, 10.08; Found: C, 60.93; H, 5.78; N, 13.23; S, 10.42.

The infrared spectrum is shown in Figure 29. This compound had an absorption maximum in the ultraviolet region at 275 millimicrons.

Hydrolysis of spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) acid---Preparation of 1-phenylpiperidine-4-carbonylthioureide.--- Five millimoles (1.45 g.) of spiro-1'-phenylpiperidine-4',5-(2--thiobarbituric) acid was suspended in 10 ml. of water and 6.4 ml. 0.78 N sodium hydroxide (5 millimoles of sodium hydroxide) was added. The acid went into solution readily. A white solid began to form almost immediately. This crude product, found to be 1-phenylpiperidine-4-carbonylthioureide, was collected with suction filtration after about 10 min. of standing and washed with two 5-ml. portions of water. The solid, which weighed 0.98 g. (75 per cent yield), was recrystallized first from hot water and then twice from ethanol, and had a m. p. of 201.5-202°.

Analysis Calculated for $C_{13}H_{16}N_3SO$: N, 16.02; S, 12.22; Found: N, 15.92; S, 12.21.

The infrared spectrum is shown in Figure 30.

Infrared Absorption Spectra

The infrared spectra reported herein were determined on a Perkin-Elmer Infracord Model 137 equipped with sodium chloride optics. In the case of liquids the spectra were made by placing a thin film of the liquid between two sodium chloride plates. For solid compounds a mull was prepared by grinding the solid with Nujol in a micro mortar; the mull was placed between sodium chloride plates for scanning. The spectra were recorded from 2.5 to 15.0 microns. The polystyrene band at 6.24 microns was recorded on each spectra and was used as a reference for wavelength calibration. The spectra are given in the Appendix.

Ultraviolet Adsorption Spectra

The ultraviolet spectra of the barbituric acids were determined using a Beckmann DK-1 recording spectrophotometer and 1-cm. quartz cells. No attempt to obtain quantitative data was made, i.e. absorbancy indexes. The spectra were determined by placing a small amount of the compound in the cell which contained 1 N sodium hydroxide and scanning as quickly as possible after mixing. The spectra of the compounds were also determined on saturated water solutions.

Vapor Phase Chromatographic Analysis

The vapor phase chromatographic analyses were conducted with a Perkin-Elmer Vapor Fractometer Model 154C. They were

run on a 6 ft. x 4 mm. copper column packed with 70/170 mesh Chromosorb P[1] which was coated with General Electric silicone gum (S. E. 30) 3 per cent by weight. The column temperature was 219° with an inlet pressure of 10 psi of helium. The flow rate under these conditions was about 60 ml./min. A single sharp symmetrical peak was interpreted to mean that a single component was present.

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[1] The author is grateful to R. G. Jones who prepared this column as per directions supplied him by Dr. C. C. Sweeley of the University of Pittsburg.

CHAPTER IV

SUMMARY

One method for the synthesis of spiropiperidine-4',-5-(2-thiobarbituric) acids was investigated briefly and found to be unsuccessful. In this method spirotetrahydropyran-4',-5-(2-thiobarbituric) acid was prepared from 4,4-dicarbethoxy-tetrahydropyran and thiourea. It was hoped to cleave the tetrahydropyran ring with hydrogen iodide and obtain 5,5-bis-(2-iodoethyl)-2-thiobarbituric acid. Condensation of this compound with primary amines should afford spiropiperidine--4',5-(2-thiobarbituric) acids; however, the cleavage reaction could not be achieved.

Two other methods were investigated with a certain amount of success for each. Both of these involved the synthesis of 1-substituted-4,4-dicarbethoxypiperidines and the condensation of these with thiourea. In one method nitrogen mustards or similar compounds were condensed with diethyl malonate in the presence of base to yield the diesters. Although good yields were obtained with bis(2-p-toluenesulfonyloxyethyl)arylamines this method was unsuccessful with bis(2-chloroethyl)amine and bis(2-p-toluenesulfonyloxyethyl)methylamine.

1-Alkyl-4,4-dicarbethoxypiperidines were obtained in the third method of synthesis. This sequence of reactions

started with ethyl isonicotinate which was alkylated at the 1-position with alkyl halides. Hydrogenation of these 1-alkyl-4-carbethoxypyridinium halides, afforded the corresponding 1-alkyl-4-carbethoxypiperidine. The latter compounds were carbethoxylated in the 4-position using triphenylmethylsodium and ethyl chloroformate.

Both the aryl and alkyl diesters condensed readily with thiourea in the presence of ethoxide to give the disodium salts of spiropiperidine-4',5-(2-thiobarbituric) acids in good yields. Neutralization with an ion exchange resin gave good yields of the 1'-aryl acids but only fair to poor yields of the 1'-alkyl acids.

The ultraviolet spectra of the new thiobarbituric acids in strong base were recorded. A hypsochromic shift was observed in the absorption of the di-anion compared to the mono-anion. Mono-anionic absorption in distilled water for the 1'-alkyl acids and none for the 1'-aryl acids indicate that the former exist as a zwitterion.

Infrared spectra were also recorded for the new compounds. These also indicate a zwitterionic structure for the 1'-alkyl acids but not for the 1'-aryl acids.

Qualitative observations indicate that the spiropiperidine thiobarbituric acids reported herein hydrolyze rapidly in basic solution.

CHAPTER V

RECOMMENDATIONS

One of the more interesting aspects of the research described herein is the carbethoxylation of 1-alkyl-4-carbethoxypiperidines. It would be of interest to carbethoxylate 1-alkyl-2- and 1-alkyl-3-carbethoxypiperidine. The conversion of the resulting 1-alkyl-2,2-dicarbethoxypiperidines and 1-alkyl-3,3-dicarbethoxypiperidines to the corresponding spiropiperidine barbituric and thiobarbituric acids would also be of interest.

Spiropiperidine thiobarbituric acids with substituents on the piperidine ring, the thiobarbituric acid ring, or both, would also be of interest to synthesize. These could be made by starting with substituted pyridine carboxylic acids to obtain substituted piperidine esters. Condensation of the diester with N-substituted thioureas should proceed readily.

Since the spiro-1'-methylpiperidine-4',5-barbituric acid prepared from 1-methyl-4,4-dicarbethoxypiperidine is different from that prepared by Daugherty, the structure of the latter should be investigated.

APPENDIX

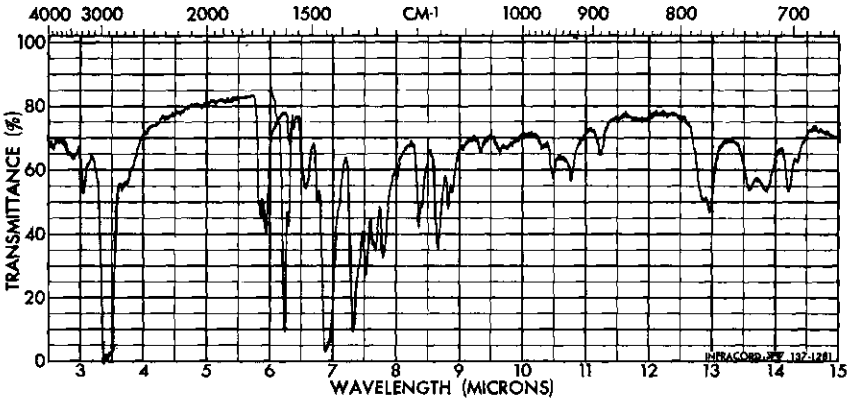

Figure 15. Infrared Spectrum of Spiro-1'-phenylpiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

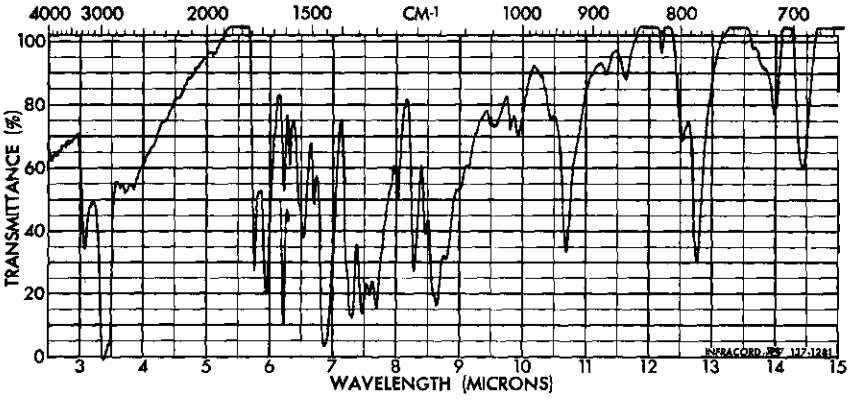

Figure 16. Infrared Spectrum of Spiro-1'-m-tolypiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

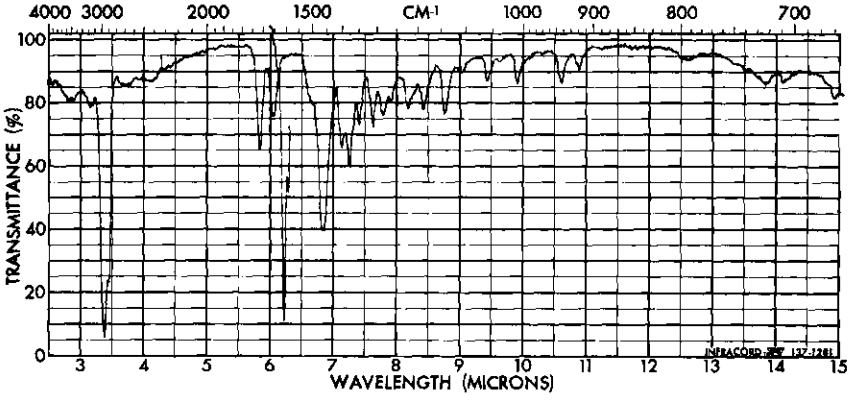

Figure 17. Infrared Spectrum of Spiro-1'-methylpiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

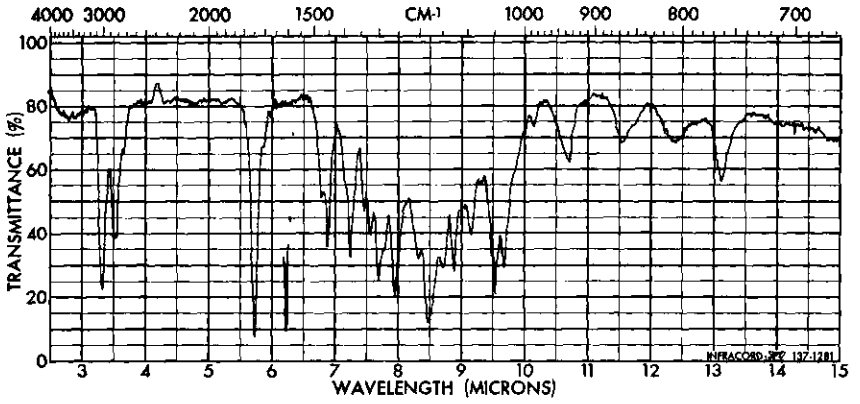

Figure 18. Infrared Spectrum of 1-Ethyl-4-carbethoxypiperidine (Liquid Film).

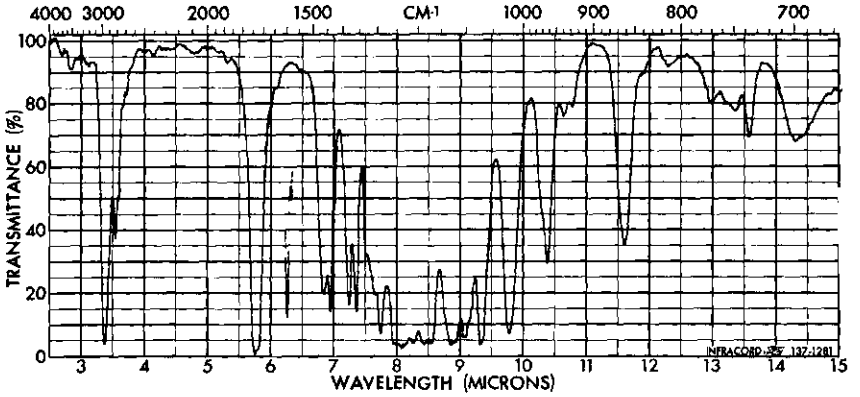

Figure 19. Infrared Spectrum of 1-Ethyl-4,4-dicarbethoxypiperidine (Liquid Film).

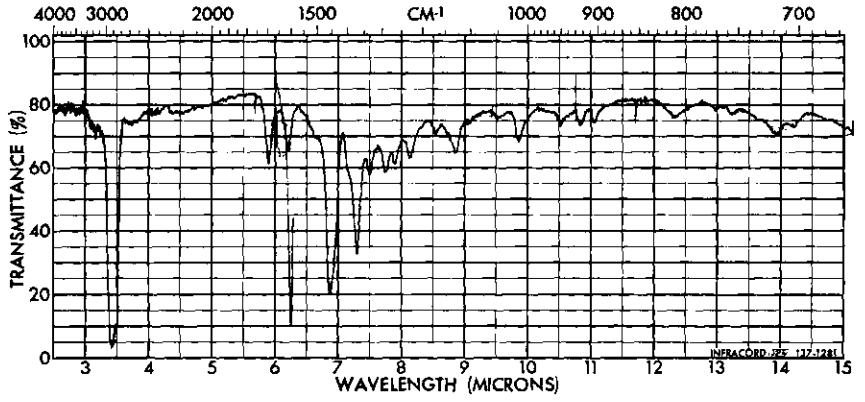

Figure 20. Infrared Spectrum of Spiro-1'-ethylpiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

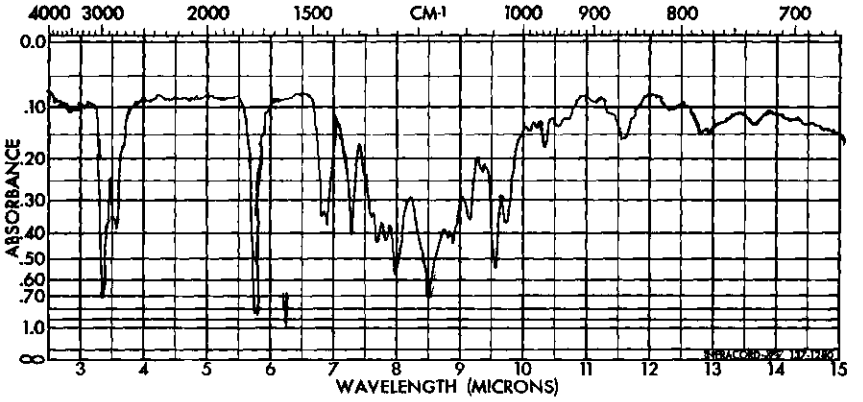

Figure 21. Infrared Spectrum of 1-n-Butyl-4-carbethoxypiperidine (Liquid Film).

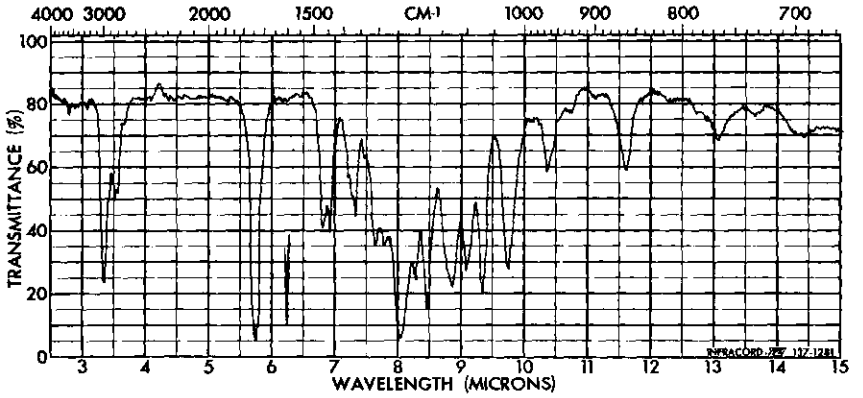

Figure 22. Infrared Spectrum of 1-n-Butyl-4,4-dicarbethoxypiperidine (Liquid Film).

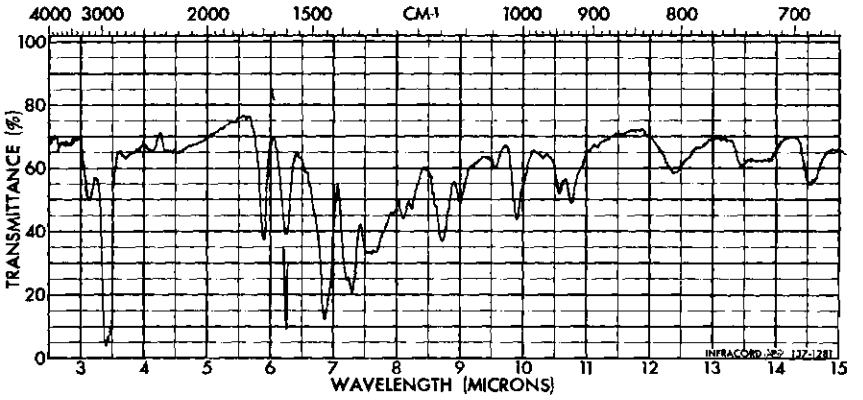

Figure 23. Infrared Spectrum of Spiro-1'-n-butylpiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

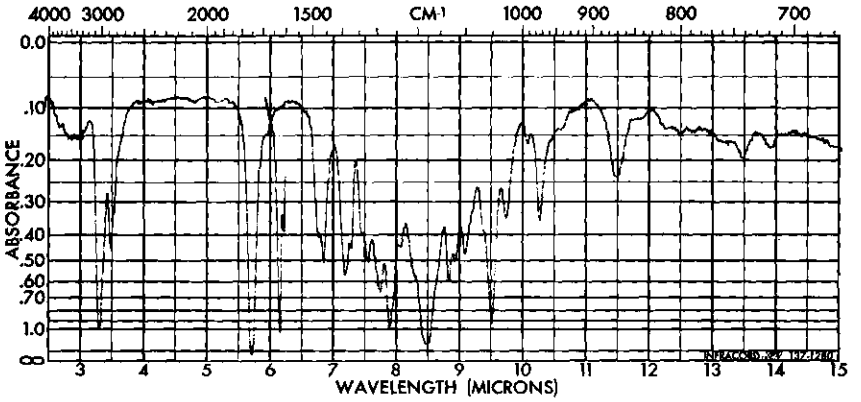

Figure 24. Infrared Spectrum of 1-iso-Propyl-4-carbethoxypiperidine (Liquid Fluid).

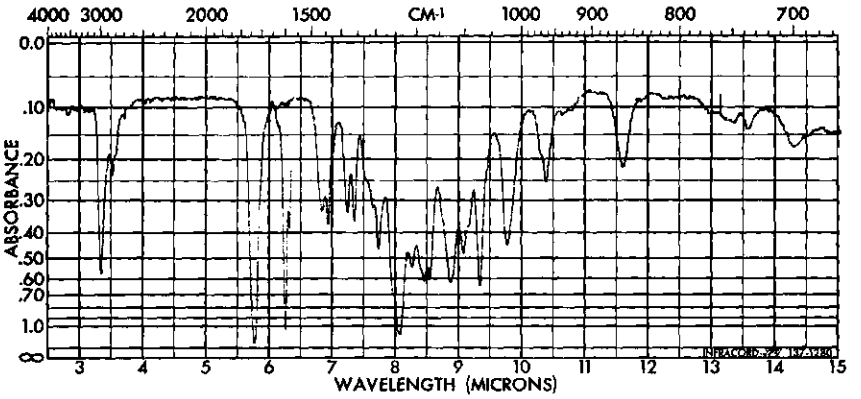

Figure 25. Infrared Spectrum of 1-iso-Propyl-4,4-dicarbethoxypiperidine (Liquid Film).

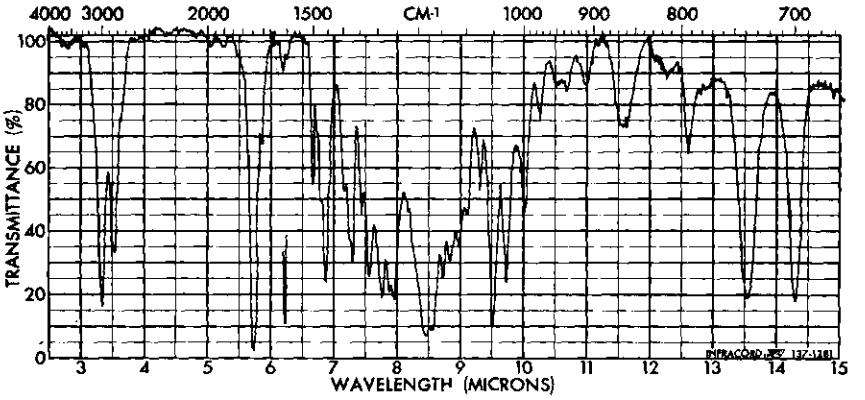

Figure 26. Infrared Spectrum of 1-Benzyl-4-carbethoxypiperidine (Liquid Film).

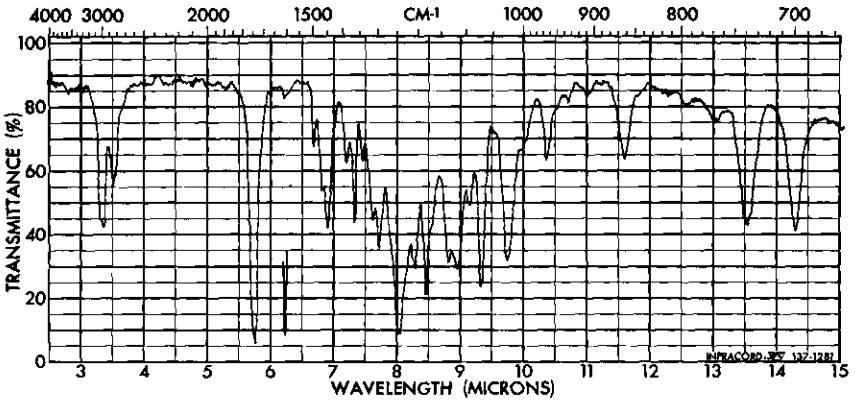

Figure 27. Infrared Spectrum of 1-Benzyl-4,4-dicarbethoxypiperidine (Liquid Film).

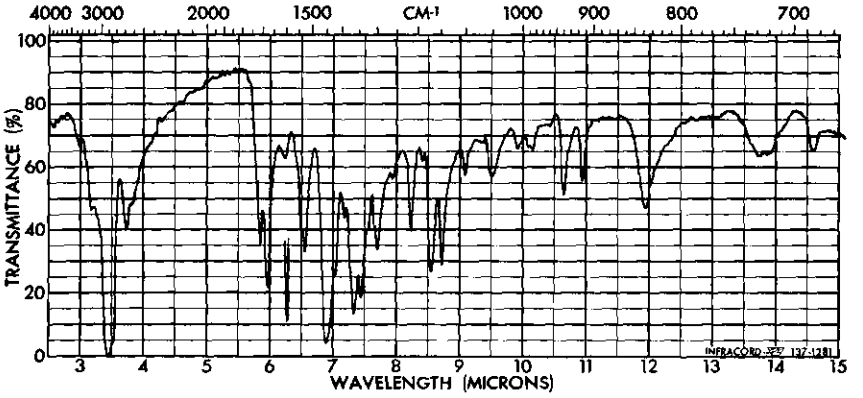

Figure 28. Infrared Spectrum of Spiro-1'-benzylpiperidine-4',5-(2-thiobarbituric) Acid (Nujol Mull).

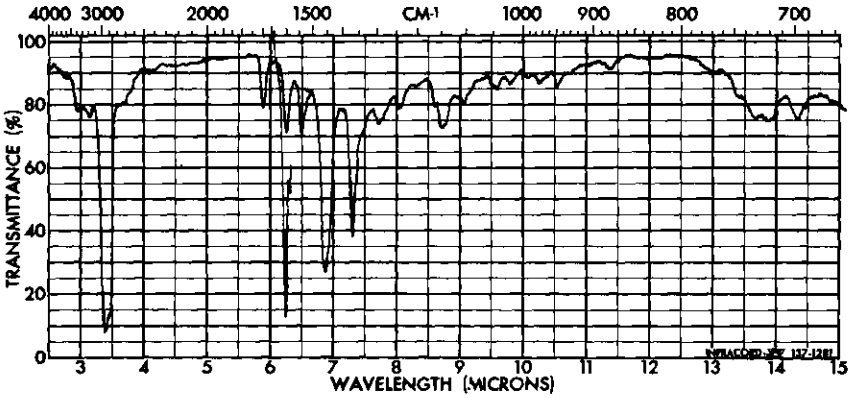

Figure 29. Infrared Spectrum of Spiro-1'-(2-phenylethyl)-piperidine-4', 5-(2-thiobarbituric) Acid (Nujol Mull).

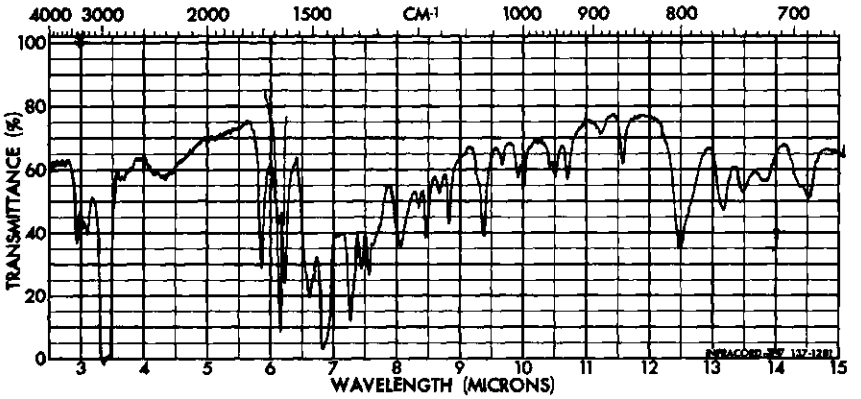

Figure 30. Infrared Spectrum of 1-Phenylpiperidine-4-carbonylthioureide (Nujol Mull).

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VITA

VITA

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